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

Mary O'Brien, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡*

Summary

Background Pembrolizumab is a standard-of-care for advanced non-small-cell lung cancer (NSCLC). We assessed pembrolizumab as adjuvant therapy for completely resected stage IB–IIIA NSCLC.

Methods In this randomised, triple-blind, phase 3 trial (PEARLS/KEYNOTE-091), patients were recruited from 196 medical centres in 29 countries. Eligible patients were aged 18 years or older, with completely resected, pathologically confirmed stage IB (tumours of ≥4 cm in diameter), II, or IIIA NSCLC per the American Joint Committee on Cancer staging system (7th edition) of any histology or PD-L1 expression level, and an Eastern Cooperative Oncology Group performance status of 0 or 1; adjuvant chemotherapy was to be considered for stage IB disease and was strongly recommended for stage II and IIIA disease, according to national and local guidelines. Using a central interactive voice-response system, eligible participants were randomly assigned (1:1), using a minimisation technique and stratified by disease stage, previous adjuvant chemotherapy, PD-L1 expression, and geographical region, to pembrolizumab 200 mg or placebo, both administered intravenously every 3 weeks for up to 18 cycles. Participants, investigators, and analysts were masked to treatment assignment. Dual primary endpoints were disease-free survival in the overall population and in the population with PD-L1 tumour proportion score (TPS) of 50% or greater. Efficacy was assessed in the intention-to-treat (ITT) population (ie, all participants randomly assigned to a treatment group). Safety was assessed in all participants randomly assigned to treatment who received at least one dose of study treatment. Here we report results of the second interim analysis, prespecified to occur when approximately 118 disease-free survival events had occurred in the PD-L1 TPS of 50% or greater population. This study is registered with ClinicalTrials.gov, NCT02504372, and is active but not recruiting.

Findings Between Jan 20, 2016, and May 6, 2020, 1177 (60%) of 1955 screened participants were randomly assigned to pembrolizumab (n=590, including n=168 with PD-L1 TPS of ≥50%) or placebo (n=587; including n=165 with PD-L1 TPS of ≥50%) and included in the ITT population. Median follow-up as of data cutoff (Sept 20, 2021) for this interim analysis was 35·6 months (IQR 27·1–45·5). In the overall population, median disease-free survival was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group versus 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63–0·91], p=0·0014). In the PD-L1 TPS of 50% or greater population, median disease-free survival was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57–1·18]; p=0·14). Grade 3 or worse adverse events occurred in 198 (34%) of 580 participants who received pembrolizumab and 150 (26%) of 581 participants who received placebo. Grade 3 or worse events that occurred in at least ten participants in either treatment group were hypertension (35 [6%]) and pneumonia (12 [2%]) with pembrolizumab and hypertension (32 [6%]) with placebo. Serious adverse events occurred in 142 (24%) participants in the pembrolizumab group and 90 (15%) in the placebo group; serious adverse events that occurred in more than 1% of participants were pneumonia (13 [2%]), pneumonitis (12 [2%]), and diarrhoea (seven [1%]) with pembrolizumab and pneumonia (nine [2%]) with placebo. Treatment-related adverse events led to death in four (1%) participants treated with pembrolizumab (one due to both cardiogenic shock and myocarditis, one due to both septic shock and myocarditis, one due to pneumonia, and one due to sudden death) and in no participants treated with placebo.

Interpretation Pembrolizumab significantly improved disease-free survival compared with placebo and was not associated with new safety signals in completely resected, PD-L1-unselected, stage IB–IIIA NSCLC. Pembrolizumab is potentially a new treatment option for stage IB–IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression.

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*Contributed equally

†Contributed equally

‡Listed in the appendix (pp 2–6)

Lung Unit, Royal Marsden Hospital, London, UK (Prof M O'Brien MD); **Hospital Universitario 12 de Octubre, CNIO, Ciberonc & Universidad Complutense, Madrid, Spain** (Prof L Paz-Ares MD); **European Organisation for Research and Treatment of Cancer, Brussels, Belgium** (S Marreaud MD, M Mauer PhD, N Jha MSc); **National and Kapodistrian University of Athens, and Frontier Science Foundation Hellas, Athens, Greece** (Prof U Dafni ScD); **North Estonia Medical Centre, Tallinn, Estonia** (K Oselin PhD); **Charles University and Thomayer Hospital, Prague, Czech Republic** (L Havel MD); **Hospital Universitario Central de Asturias, Oviedo, Spain** (Prof E Esteban MD); **University Hospital Lozano Blesa, IIS Aragon, Zaragoza, Spain** (D Isla MD); **Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain** (A Martinez-Marti MD); **Klinikum Esslingen, Esslingen, Germany** (M Faehling MD); **National Cancer Center Hospital East, Kashiwa, Japan** (Prof M Tsuboi MD); **Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea** (Prof J-S Lee MD); **Kindai University Faculty of Medicine, Osaka, Japan** (Prof K Nakagawa MD); **Merck & Co, Rahway, NJ, USA**

(J Yang PhD, A Samkari MD, S M Keller MD); **ETOP IBCSG Partners Foundation, Berne, Switzerland** (Prof R Stahel MD); **Paris Saclay University, Institut Gustave Roussy, Villejuif, France** (Prof B Besse MD); **Lausanne University Hospital, Lausanne, Switzerland** (Prof S Peters MD)

Correspondence to: Prof Mary O'Brien, Lung Unit, Royal Marsden Hospital, Sutton, Surrey, SM2 5PT, UK
mary.obrien@rmh.nhs.uk

See Online for appendix

Introduction

For patients with stage IB (tumours of ≥4 cm in diameter) to IIIA non-small-cell lung cancer (NSCLC), per the American Joint Committee on Cancer (AJCC) staging system (7th edition), standard treatment is resection followed by adjuvant therapy with platinum-based chemotherapy.[1–4] Although adjuvant chemotherapy improves overall survival in completely resected NSCLC, the absolute 5-year survival benefit is moderate compared with observation alone.[5,6] Until recently, efforts to improve the efficacy of platinum-based chemotherapy in the adjuvant setting were unsuccessful. In ADAURA,[7] an improvement in disease-free survival was seen with the EGFR inhibitor osimertinib compared with placebo when given after complete resection and, at the discretion of the physician and patient, adjuvant chemotherapy in stage IB–IIIA, *EGFR*-mutation-positive NSCLC. In IMpower010,[8] the PD-L1 inhibitor atezolizumab given after complete resection and adjuvant chemotherapy improved disease-free survival compared with best supportive care in stage II–IIIA NSCLC that expressed PD-L1 on at least 1% of tumour cells.

The PD-1 inhibitor pembrolizumab has become a standard of care for locally advanced or metastatic NSCLC because of its demonstrated survival benefit and manageable safety profile.[4,9,10] Pembrolizumab with concurrent chemoradiotherapy has also shown efficacy and manageable toxicity in unresectable, locally advanced, stage III NSCLC.[11] In EORTC-1416-LCG/ETOP 8-15–PEARLS/KEYNOTE-091 (hereafter referred to as PEARLS/KEYNOTE-091), we compared pembrolizumab with placebo as adjuvant therapy for completely resected stage IB–IIIA NSCLC.

Methods

Study design and participants

PEARLS/KEYNOTE-091 is a randomised, triple-blind, phase 3 study that was run at 196 medical centres in 29 countries (appendix pp 2–6). Enrolment in the study was done in three parts: registration, PD-L1 assessment, and randomisation. Participants were enrolled by study investigators. Registration was done centrally at the European Organisation for Research and Treatment of Cancer (EORTC) headquarters (Brussels, Belgium).

Participants eligible for registration were aged 18 years or older, provided written informed consent for tumour testing, had pathologically confirmed NSCLC (any histology) of stage IB (tumours of ≥4 cm in diameter), II, or IIIA per the AJCC staging system (7th edition) after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy) including negative margins (R0), and had an available tumour sample

Research in context

Evidence before this study

We searched PubMed on April 27, 2022, for English-language publications of randomised, controlled trials published since database inception using the terms ("PD-1 inhibitor" OR "PD-L1 inhibitor" OR "checkpoint inhibitor" OR "atezolizumab" OR "cemiplimab" OR "durvalumab" OR "nivolumab" OR "pembrolizumab") AND ("adjuvant" OR "early-stage" OR "resected" OR "stage IB-IIIA") AND ("non-small-cell lung cancer" OR "NSCLC"). We also searched abstracts from the 2019, 2020, and 2021 American Association for Cancer Research Annual Meetings; 2019, 2020, and 2021 American Society of Clinical Oncology (ASCO) Annual Meetings; 2021 ASCO Monthly Plenary Series; 2019, 2020, and 2021 European Society of Medical Oncology (ESMO) Congresses; 2021 ESMO Virtual Plenaries; and 2019, 2020, and 2021 World Conferences on Lung Cancer using the same search terms. The only other published data from a randomised, controlled trial that we identified was from a multicentre, randomised, open-label, phase 3 trial, IMpower010. In IMpower010, the PD-L1 inhibitor atezolizumab significantly improved disease-free survival versus best supportive care after adjuvant chemotherapy in participants with completely resected stage II–IIIA non-small-cell lung cancer (NSCLC), with a more pronounced benefit in participants with PD-L1 expression on 1% or more of tumour cells; atezolizumab did not significantly improve disease-free survival in the overall stage IB (tumours of ≥4 cm in diameter) to IIIA population.

Added value of this study

To our knowledge, PEARLS/KEYNOTE-091 is the first placebo-controlled trial to find a significant improvement in disease-free survival for a checkpoint inhibitor and the first trial to show a disease-free survival benefit in a PD-L1-unselected population of patients with completely resected stage IB (tumours of ≥4 cm in diameter)–IIIA NSCLC who received adjuvant chemotherapy per local guidelines. The disease-free survival benefit of pembrolizumab was generally similar across subgroups based on PD-L1 expression. The adverse event profile seen in participants treated with pembrolizumab was consistent with that previously reported for pembrolizumab.

Implications of all the available evidence

PEARLS/KEYNOTE-091 adds to the body of evidence supporting the value of checkpoint inhibitors, specifically those that target the PD-1–PD-L1 pathway, in the adjuvant treatment of early-stage NSCLC. Longer follow-up is necessary to determine whether checkpoint inhibitors significantly prolong overall survival in this setting. Our findings support pembrolizumab as a potential new treatment option for patients with stage IB, II, or IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression.

obtained during resection for PD-L1 assessment. Systematic complete or lobe-specific mediastinal lymph node dissection was recommended; at a minimum, the subcarinal (level 7) and a lobe-specific node must have been examined to establish the absence of N2 disease. Key eligibility criteria for randomisation were known PD-L1 expression status determined in part two, written informed consent for study participation, no evidence of disease on clinical examination and radiographic assessment per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1,[12] assessed by local review after surgery but within 12 weeks before randomisation, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function within 10 days of treatment initiation, assessed via absolute neutrophil count, platelet count, haemoglobin concentration, and concentrations of creatinine, total bilirubin, alanine aminotransferase, and aspartate aminotransferase. Previous neoadjuvant or adjuvant radiotherapy for the current malignancy was not permitted. Adjuvant chemotherapy was not mandatory but was to be considered for patients with stage IB disease and strongly recommended for those with stage II and IIIA disease, according to national and local guidelines. Participants without previous adjuvant chemotherapy were to receive their first study treatment administration within 12 weeks of surgery. Participants who received adjuvant chemotherapy were to receive no more than four chemotherapy cycles initiated within 12 weeks of surgery and receive their first study treatment administration at least 3 weeks but no more than 12 weeks from the last chemotherapy dose. Patients with a history of HIV, those with active hepatitis B or C infection, and those with active autoimmune disease requiring treatment within the past 2 years were also ineligible. Full eligibility criteria are available in the protocol (appendix).

The study protocol and its amendments (appendix) were approved by the appropriate local or national ethics body for each participating centre. An independent data and safety monitoring committee oversaw the trial, assessed safety every 6 months, and assessed efficacy at prespecified interim analyses. Here, we report the protocol-specified second interim analysis of this study.

Randomisation and masking

Based on a minimisation technique[13] with a random allocation component to ensure 15% of completely random assignments, eligible participants were randomly assigned (1:1) using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA) to receive pembrolizumab or placebo. The randomisation list was generated by Almac Clinical Technologies; randomisation numbers were scrambled to ensure concealment of treatment assignment. The randomisation was stratified by disease stage (IB *vs* II *vs* IIIA), receipt of adjuvant chemotherapy (yes *vs* no), PD-L1 tumour proportion score (TPS; percentage of tumour cells with membranous PD-L1 staining; <1% *vs* 1–49% *vs* ≥50%), and geographical region (Asia *vs* eastern Europe *vs* western Europe *vs* the rest of the world). The minimisation algorithm was applied separately to each PD-L1 TPS to optimise the balance of treatment groups within each TPS. Participants, investigators, and those collecting or analysing the data were masked to treatment assignment, including representatives of the sponsor and EORTC and European Thoracic Oncology Platform (ETOP) headquarters teams. Local pharmacists were aware of assignments.

Procedures

After randomisation, participants received either pembrolizumab 200 mg or saline placebo administered intravenously once every 3 weeks until recurrence assessed per RECIST version 1.1[12] by investigator review, new malignancy, unacceptable toxicity, investigator decision, consent withdrawal, completion of 18 administrations (approximately 1 year of treatment), or other reason (full details are in the protocol [appendix]). Participants who stopped study treatment continued to be followed up as part of the study unless they withdrew consent. Crossover from placebo to pembrolizumab was not permitted. Full details regarding treatment decisions, including guidelines for interruption and discontinuation to manage adverse events (dose reductions were not permitted), are in the protocol (appendix).

PD-L1 TPS was determined using formalin-fixed paraffin-embedded tumour tissue at a central laboratory (Q² Solutions Europe, Livingston, UK) using PD-L1 IHC 22C3 pharmDx (Agilent Technologies; Carpinteria, CA, USA). *EGFR* mutation and *ALK* rearrangement status were assessed locally at the discretion of the investigator (known status was not required for enrolment). Contrast-enhanced chest and upper abdomen CT scans were done within 12 weeks before randomisation, 12 weeks after the first study treatment administration, and every 12 weeks thereafter for year 1, every 6 months during years 2 and 3, annually in years 4 and 5, and per local standard of care thereafter until disease recurrence or withdrawal of consent; the protocol allowed additional imaging to be done as clinically indicated. Contrast-enhanced CT or MRI scans of the brain were done within 12 weeks before randomisation and only if clinically indicated thereafter. After treatment discontinuation, survival was assessed every 12 weeks up to year 5 and every 6 months thereafter.

Physical examinations and laboratory, haematology, and chemistry analyses were done regularly during and at the end of treatment (protocol [appendix]). Adverse events and laboratory abnormalities were assessed regularly throughout treatment and up to 30 days after the last treatment administration (≤90 days for serious events and events of interest in the absence of new anticancer therapy), classified according to the Medical

Dictionary for Regulatory Activities (version 24.0), and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). Adverse events of interest were based on a list of terms prepared by the sponsor and included events that were potentially immune-mediated and infusion reactions, regardless of attribution to study treatment by the investigator.

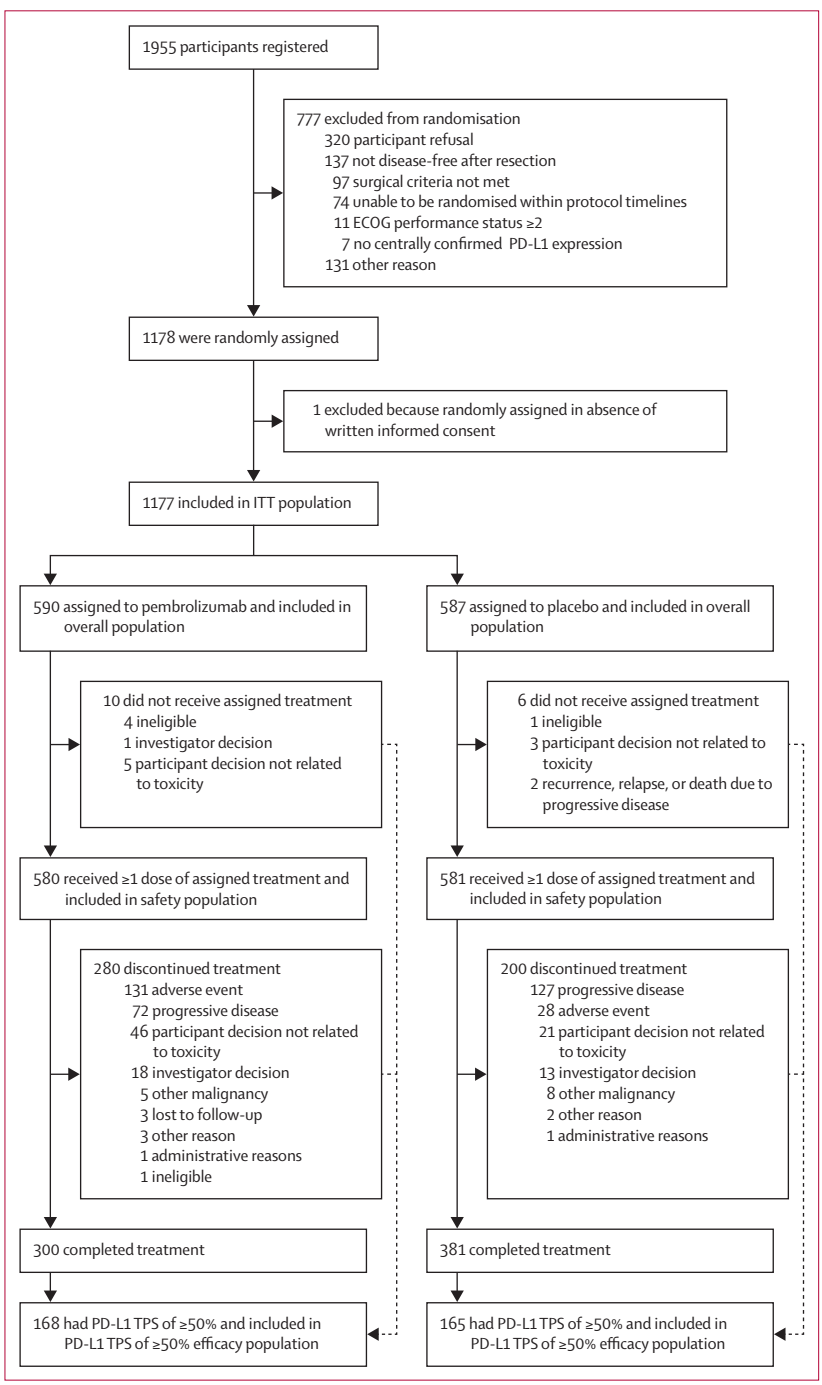

Figure 1: **Study profile**
No study data were collected for the participant excluded from the ITT population, who was randomly assigned in the absence of written informed consent. ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. PD=progressive disease. TPS=tumour proportion score.

Outcomes

The dual primary endpoints were disease-free survival in the overall population and in the PD-L1 TPS of 50% or greater population (referred to as the PD-L1 strong positive population in the protocol).

Secondary endpoints were disease-free survival in the PD-L1 TPS of 1% or greater population; overall survival in the overall population, PD-L1 TPS of 50% or greater population, and PD-L1 TPS of 1% or greater population; lung cancer-specific survival in the overall population; and safety. Disease-free survival was defined as time from randomisation to locoregional or metastatic recurrence assessed per RECIST version 1.1[12] by investigator review, appearance of a second NSCLC primary or other malignancy, or death from any cause, whichever occurred first. Overall survival was defined as time from randomisation to death from any cause. Lung cancer-specific survival was defined as time from randomisation to death due to lung cancer as determined by the investigator. The secondary endpoints of disease-free survival in the PD-L1 TPS of 1% or greater population, overall survival in the PD-L1 TPS of 50% or greater and 1% or greater populations, and lung cancer-specific survival in the overall population will be reported in future publications, in accordance with the statistical analysis plan.

Prespecified exploratory endpoints will be presented in future publications.

Statistical analysis

The statistical analysis plan is in the protocol (appendix). Efficacy was assessed in the intention-to-treat (ITT) population, defined as all participants randomly assigned to a treatment group. Safety was assessed in all randomly assigned participants who received at least one study treatment administration.

The study was designed to enrol approximately 1180 participants. The family-wise type 1 error rate was strictly controlled at a one-sided α of 0·025 for all disease-free and overall survival hypotheses using the graphical method of Maurer and Bretz.[14] The initial α allocation was 0·0125 to test disease-free survival in the overall population and 0·0125 to test disease-free survival in the PD-L1 TPS of 50% or greater population; per the multiplicity graph for α re-allocation (appendix p 7), if significance was found for disease-free survival in the overall population, overall survival could be tested. We used the Hwang-Shih-DeCani spending function, with gamma equal to –4, to control the type 1 error across all planned interim analyses and the final analysis. The trial has approximately 86% power at an α level of 0·0125 to detect a hazard ratio (HR) for disease-free survival of 0·75 in the overall population (corresponding to median disease-free survival of 56 months in the

pembrolizumab group and 42 months in the placebo group) and approximately 90% power at an α level of 0·0125 to detect an HR for disease-free survival of 0·55 in the PD-L1 TPS of 50% or greater population (corresponding to median disease-free survival of 76·4 months in the pembrolizumab group and 42 months in the placebo group).

The independent data and safety monitoring committee reviewed results of the protocol-specified first interim analysis and recommended the trial continue as planned. The second interim analysis, results of which are reported here, was to be done when approximately 118 disease-free survival events had occurred in the PD-L1 TPS of 50% or greater population. The significance boundary for disease-free survival in the overall population for this interim analysis was p=0·0056. The proportional hazards assumption for the treatment effect was assessed using the score test based on Schoenfeld residuals.[15]

We estimated disease-free and overall survival using the Kaplan-Meier method, with 24 and 36 months being timepoints of interest at this interim analysis. We censored data for participants without a disease-free survival event on the date of their last disease assessment. We considered participants found to have recurrence before randomisation to have an event on the date of randomisation for the primary analysis. In a protocol-specified sensitivity analysis, data for these participants were censored on the date of randomisation. For analysis of overall survival, we censored data for participants without a death date on the date they were last known to be alive.

We assessed treatment comparisons using the permutation test for disease-free survival[16] and the Wald test for overall survival on the basis of a multivariate Cox proportional hazards model adjusted for the stratification factors at randomisation and the additional factors of histology (squamous *vs* non-squamous) and smoking status (never *vs* former or current). We calculated adjusted HRs and, per protocol, associated 95% CIs using the same multivariate Cox model. Ties were handled by Efron's method. We also did a prespecified analysis of disease-free survival in subgroups of the overall population on the basis of the stratification factors, histology (squamous *vs* non-squamous), smoking status (never *vs* former *vs* current), sex (male *vs* female), age (<65 *vs* ≥65 years), ECOG performance status (0 *vs* 1), face (White *vs* all others), and *EGFR* mutation (yes *vs* no *vs* unknown). We only did these subgroup analyses for subgroups that had at least 50 participants in all groups. We did these subgroup analyses using a univariate Cox model with treatment as a single covariate, with the exception of PD-L1 TPS subgroup analyses, for which we used the aforementioned multivariate Cox model.

We calculated the difference in risk between treatment groups for adverse events that occurred in more than 10% of participants in either group, for adverse events of grade 3 or worse that occurred in more than

	Overall intention-to-treat population		PD-L1 TPS of ≥50% population	
	Pembrolizumab group (n=590)	Placebo group (n=587)	Pembrolizumab group (n=168)	Placebo group (n=165)
Age, years	65·0 (59·0–70·0)	65·0 (59·0–70·0)	64·5 (60·0–69·5)	65·0 (58·0–71·0)
<65	285 (48%)	273 (47%)	84 (50%)	82 (50%)
≥65	305 (52%)	314 (53%)	84 (50%)	83 (50%)
Sex				
Female	189 (32%)	184 (31%)	47 (28%)	49 (30%)
Male	401 (68%)	403 (69%)	121 (72%)	116 (70%)
Race				
American Indian or Alaskan Native	1 (<1%)	0	1 (1%)	0
Asian	107 (18%)	107 (18%)	29 (17%)	29 (18%)
Black or African American	0	3 (1%)	0	0
Multiple	4 (1%)	1 (<1%)	0	1 (1%)
Other	6 (1%)	2 (<1%)	3 (2%)	1 (1%)
White	450 (76%)	455 (78%)	128 (76%)	127 (77%)
Missing	22 (4%)	19 (3%)	7 (4%)	7 (4%)
Geographical region				
Asia	106 (18%)	105 (18%)	29 (17%)	29 (18%)
Eastern Europe	116 (20%)	113 (19%)	31 (18%)	30 (18%)
Western Europe	303 (51%)	301 (51%)	90 (54%)	89 (54%)
Rest of the world	65 (11%)	68 (12%)	18 (11%)	17 (10%)
ECOG performance status				
0	380 (64%)	343 (58%)	116 (69%)	101 (61%)
1	210 (36%)	244 (42%)	52 (31%)	64 (39%)
Smoking status				
Current	75 (13%)	90 (15%)	24 (14%)	29 (18%)
Former	428 (73%)	431 (73%)	130 (77%)	123 (75%)
Never	87 (15%)	66 (11%)	14 (8%)	13 (8%)
Histology				
Non-squamous	398 (67%)	363 (62%)	103 (61%)	105 (64%)
Squamous	192 (33%)	224 (38%)	65 (39%)	60 (36%)
Disease stage				
IB	84 (14%)	85 (14%)	21 (13%)	22 (13%)
II	329 (56%)	338 (58%)	95 (57%)	93 (56%)
IIIA	177 (30%)	162 (28%)	52 (31%)	50 (30%)
IV	0	2 (<1%)*	0	0
Regional lymph node stage (pN)				
N0	233 (39%)	257 (44%)	47 (28%)	59 (36%)
N1	233 (39%)	223 (38%)	84 (50%)	72 (44%)
N2	124 (21%)	107 (18%)	37 (22%)	34 (21%)
Received adjuvant chemotherapy				
No	84 (14%)	83 (14%)	25 (15%)	24 (15%)
Yes†	506 (86%)	504 (86%)	143 (85%)	141 (85%)
1–2 cycles	35 (6%)	32 (5%)	8 (5%)	8 (5%)
3–4 cycles	471 (80%)	472 (80%)	135 (80%)	133 (81%)
PD-L1 TPS				
<1%	233 (39%)	232 (40%)	0	0
1–49%	189 (32%)	190 (32%)	0	0
≥50%	168 (28%)	165 (28%)	168 (100%)	165 (100%)

(Table 1 continues on next page)

	Overall intention-to-treat population		PD-L1 TPS of ≥50% population	
	Pembrolizumab group (n=590)	Placebo group (n=587)	Pembrolizumab group (n=168)	Placebo group (n=165)
(Continued from previous page)				
EGFR mutation‡				
No	218 (37%)	216 (37%)	57 (34%)	67 (41%)
Yes	39 (7%)	34 (6%)	6 (4%)	5 (3%)
Unknown	333 (56%)	337 (57%)	105 (63%)	93 (56%)
ALK translocation‡				
No	226 (38%)	190 (32%)	55 (33%)	58 (35%)
Yes	7 (1%)	7 (1%)	3 (2%)	0
Unknown	357 (61%)	390 (66%)	110 (65%)	107 (65%)

Data are median (IQR) or n (%). Some proportions might add up to more than 100% due to rounding. Data for the stratification factors of disease stage, receipt of adjuvant chemotherapy, and region of enrolment are based on actual data. Data for the stratification factor of PD-L1 TPS are based on data held by Almac Clinical Technologies, who created the randomisation sequence. ECOG=Eastern Cooperative Oncology Group. TPS=tumour proportion score. *Metastatic disease was discovered soon after randomisation upon review of additional protocol-required screening CT images in one participant and of a non-protocol-required lumbar MRI assessment in the second participant; because of ineligibility, both participants were discontinued from active study treatment before the first administration but were included in the intention-to-treat population. †All participants received either a cisplatin-based regimen, a carboplatin-based regimen, or a cisplatin-based and carboplatin-based regimen. Of all participants allocated to treatment with pembrolizumab versus placebo, 301 (51%) of 590 versus 307 (52%) of 587 received a cisplatin-based regimen only, 184 (31%) versus 171 (29%) received a carboplatin-based regimen only, and 21 (4%) versus 26 (4%) received both a cisplatin-based and carboplatin-based regimen. ‡Known *EGFR* mutation and *ALK* translocation status were not required for trial entry.

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

1% of participants in either group, and for serious adverse events that occurred in more than 1% of participants in either group. We calculated 95% CIs for the risk differences using the unstratified Miettinen and Nurminen method.

We did all statistical analyses using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02504372, and is ongoing but closed to enrolment.

Role of the funding source

The funder of the study, in collaboration with representatives of the EORTC Lung Cancer Group and ETOP, participated in study design, data analysis, data interpretation, and writing of this report. The funder had no role in data collection. EORTC maintained the study database.

Results

Between Jan 20, 2016, and May 6, 2020, of 1955 registered participants, 1178 were randomly assigned to treatment (figure 1). One participant was randomly assigned to treatment in error due to an administrative issue and was excluded from all analyses, leaving 1177 participants in the overall ITT population: 590 randomly assigned to pembrolizumab and 587 to placebo (figure 1). The PD-L1 TPS of 50% or greater ITT population included 333 (28%) of 1177 participants, 168 (50%) of 333 were in the pembrolizumab group and 165 (50%) were in the placebo group. Baseline characteristics were generally balanced between treatment groups in the overall and PD-L1 TPS of 50% or greater populations (table 1). Median age in the overall ITT population was 65 years (IQR 59–70) and in the PD-L1 TPS of 50% or greater population was 65 years (59–70). In the overall ITT population, 373 (32%) were women and 804 (68%) were men, and in the PD-L1 TPS of 50% or greater ITT population, 96 (29%) were women and 237 (71%) were men. Most participants received three or four cycles of previous adjuvant chemotherapy with a cisplatin-based or carboplatin-based regimen, or both.

Median follow-up (ie, time from randomisation to data cutoff on Sept 20, 2021) for this second interim analysis was 35·6 months (IQR 27·1–45·5). Among the 1161 participants in the safety population, 300 (52%) of 580 in the pembrolizumab group and 381 (66%) of 581 in the placebo group completed treatment (figure 1); the remaining 280 (48%) participants in the pembrolizumab group and 200 (34%) in the placebo group had discontinued treatment before receiving 18 administrations. The median number of study treatment administrations was 17 (IQR 6–18) in the pembrolizumab group and 18 (13–18) in the placebo group. Median treatment duration was 11·7 months (IQR 4·2–12·0) in the pembrolizumab group and 11·8 months (8·3–12·0) in the placebo group. The most common reason for treatment discontinuation was adverse events in the pembrolizumab group and progressive disease in the placebo group (figure 1).

In the overall population, 212 (36%) of 590 participants in the pembrolizumab group and 260 (44%) of 587 in the placebo group had a disease-free survival event as of data cutoff. Median disease-free survival was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group versus 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63–0·91], p=0·0014; figure 2A). In the PD-L1 TPS of 50% or greater population, 54 (32%) of 168 participants in the pembrolizumab group and 63 (38%) of 165 in the placebo group had a disease-free survival event. Median disease-free survival was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57–1·18]; p=0·14; figure 2B). Recurrence was the most common disease-free survival event in both populations (appendix p 11). The proportional hazards assumption for the treatment effect was not violated for either the overall (p=0·27) or PD-L1 TPS of 50% or greater (p=0·55) population. Disease-free survival in subgroups of the overall population is shown in figure 2C. Kaplan-Meier curves of disease-free survival in the PD-L1 TPS of 50% or greater, 1–49%, and less than 1% populations are in the appendix (p 8).

Retrospective review identified that seven (1%) of 590 participants in the pembrolizumab group and four (1%) of 587 participants in the placebo group (two [1%] of 168 in the pembrolizumab group and none of 165 in the placebo group of the PD-L1 TPS of ≥50% population) had disease recurrence before randomisation. In a protocol-specified sensitivity analysis in which these participants were censored on the randomisation date, the HR for

disease-free survival was 0·74 (95% CI 0·62–0·89) in the overall population and 0·79 (95% CI 0·54–1·14) in the PD-L1 TPS of 50% or greater population (appendix p 9).

In the overall population, 98 (17%) of 590 participants in the pembrolizumab group and 111 (19%) of 587 participants in the placebo group had died as of data

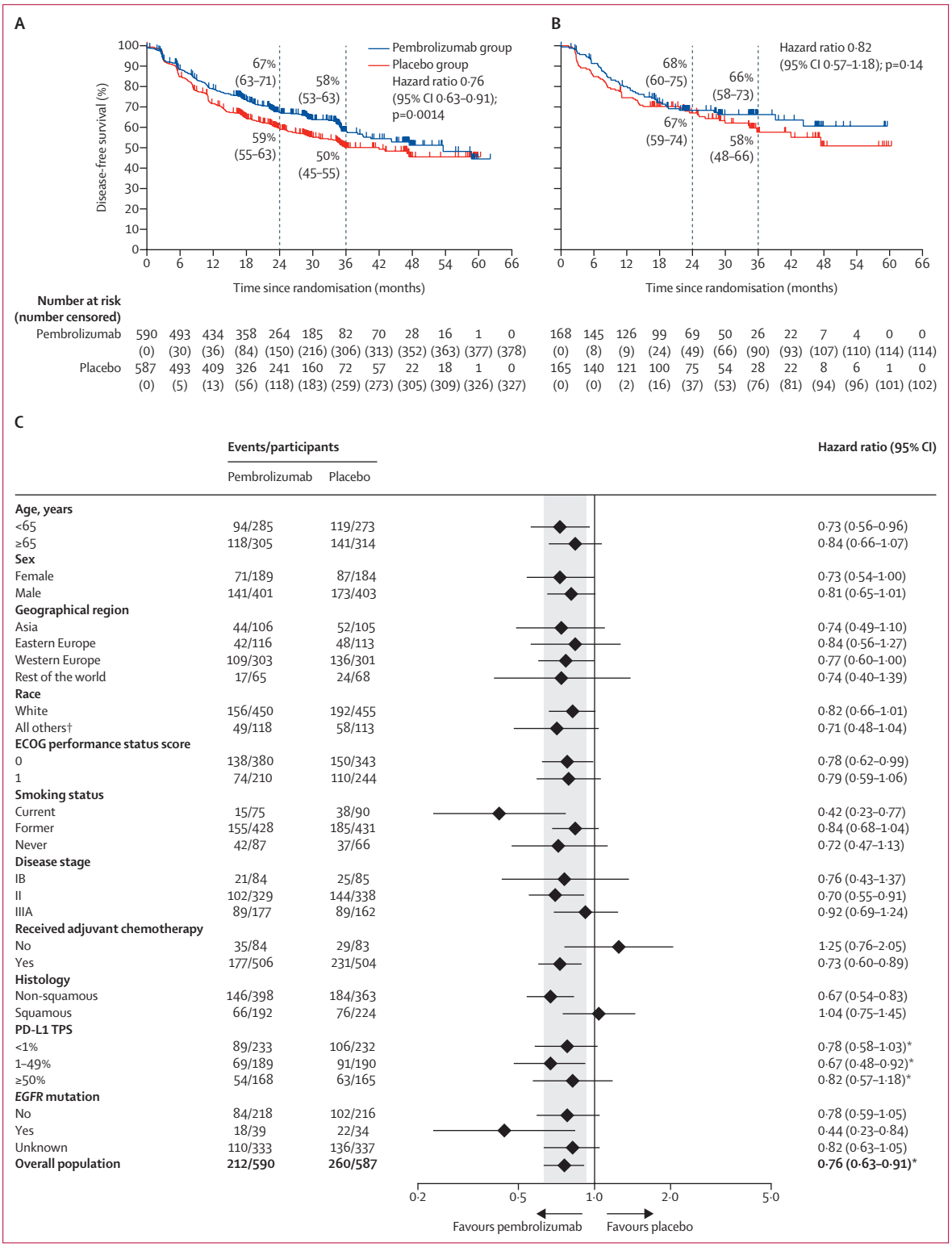

Figure 2: **Disease-free survival in the intention-to-treat population**
Kaplan-Meier estimates of disease-free survival assessed per RECIST version 1.1 by investigator review are shown for (A) the overall population and (B) the PD-L1 TPS of 50% or greater population.
(C) Disease-free survival in subgroups of the overall population that included at least 50 participants, with the vertical grey shaded band indicating the 95% CI for the overall population.
ECOG=Eastern Cooperative Oncology Group. RECIST=Response Evaluation Criteria in Solid Tumours. TPS=tumour proportion score. *Hazard ratios are adjusted for the stratification factors at randomisation and the additional factors of histology (squamous *vs* non-squamous) and smoking status (never *vs* former or current); all other hazard ratios and associated 95% CIs were derived from a univariate Cox model with treatment as a single covariate. †Includes the race categories of American Indian or Alaskan Native, Asian, Black or African American, multiple, and other.

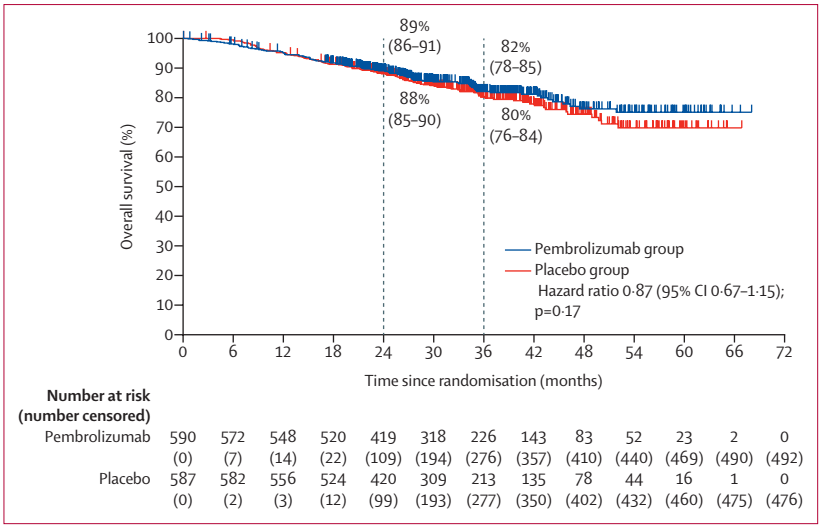

Figure 3: **Kaplan-Meier estimate of overall survival in the intention-to-treat population**
Tick marks indicate censored data.

cutoff. Median overall survival (and 95% CI) was not reached in either group (HR 0·87 [95% CI 0·67–1·15], p=0·17; figure 3).

In the safety population, adverse events of any grade and cause occurred in 556 (96%) of 580 participants treated with pembrolizumab and 529 (91%) of 581 treated with placebo (table 2); grade 3 or worse adverse events occurred in 198 (34%) participants in the pembrolizumab group and 150 (26%) in the placebo group (a full accounting of all grade 3, 4, and 5 adverse events is in the appendix [pp 12–16]). Adverse events led to treatment discontinuation in 115 (20%) participants treated with pembrolizumab and in 34 (6%) treated with placebo (appendix p 17) and treatment interruption in 221 (38%) in the pembrolizumab group and 145 (25%) in the placebo group (appendix pp 18–19). Adverse events led to death in 11 (2%) participants treated with pembrolizumab and six (1%) treated with placebo (appendix p 20). Four (1%) participants treated with pembrolizumab died due to events attributed to treatment by the investigator: one due to both cardiogenic shock and myocarditis, one due to both septic shock and myocarditis, one due to pneumonia, and one due to sudden death. No deaths were attributed to treatment in the placebo group.

The most common adverse events of any grade were increased bodyweight, pruritus, and hypothyroidism in the pembrolizumab group and increased bodyweight, cough, and fatigue in the placebo group (table 2). Among events that occurred in at least 10% of participants in either group, participants in the pembrolizumab group had a greater risk of hypothyroidism, pruritus, hyperthyroidism, and arthralgia than did those in the placebo group, whereas participants in the placebo group had a greater risk of increased bodyweight than did those in the pembrolizumab group (appendix p 10). Grade 3 or worse adverse events that occurred in at least 2% of participants were hypertension (35 [6%]) and pneumonia (12 [2%]) in the pembrolizumab group and hypertension (32 [6%]) and increased bodyweight (nine [2%]) in the placebo group (appendix pp 12–16), none of which were of greater risk in one treatment group than the other (appendix p 10). Serious adverse events occurred in 142 (24%) participants treated with pembrolizumab and 90 (15%) treated with placebo; serious events that occurred in more than 1% of participants were pneumonia (13 [2%]), pneumonitis (12 [2%]), and diarrhoea (seven [1%]) in the pembrolizumab group and pneumonia (nine [2%]) in the placebo group, and there was a greater risk of diarrhoea in the pembrolizumab group than in the placebo group (appendix p 10).

Adverse events attributed to treatment by the investigator occurred in 436 (75%) of 580 participants treated with pembrolizumab and 305 (52%) of 581 participants treated with placebo, and led to treatment discontinuation in 98 (17%) in the pembrolizumab group and 20 (3%) in the placebo group (appendix pp 21–23). Any-grade treatment-related adverse events that occurred in at least 10% of participants were hypothyroidism (114 [20%]), pruritus (104 [18%]), diarrhoea (74 [13%]), and fatigue (61 [11%]) in the pembrolizumab group and pruritus (60 [10%]) in the placebo group (appendix pp 21–22). Grade 3 or worse treatment-related adverse events occurred in 88 (15%) participants in the pembrolizumab group and 25 (4%) in the placebo group. There were two grade 3 or worse treatment-related adverse events that occurred in at least five participants, both in the pembrolizumab group: pneumonitis (seven [1%]) and diarrhoea (six [1%]; appendix pp 21–22). Treatment-related serious adverse events occurred in 68 (12%) participants in the pembrolizumab group, most commonly pneumonitis (12 [2%]) and diarrhoea (six [1%]), and in 13 (2%) participants in the placebo group, most commonly pneumonitis (three [1%]) and colitis (two [<1%]; appendix p 24).

Potentially immune-mediated adverse events and infusion reactions occurred in 226 (39%) of 580 participants treated with pembrolizumab and 75 (13%) of 581 participants treated with placebo, including 46 (8%) in the pembrolizumab group and 11 (2%) in the placebo group who had grade 3 or worse events (table 3). Of these participants, 84 (37%) of 226 in the pembrolizumab group and 17 (23%) of 75 in the placebo group received corticosteroids. Potentially immune-mediated adverse events that occurred in at least 5% of participants treated with pembrolizumab were hypothyroidism, hyperthyroidism, and pneumonitis; grade 3 or worse immune-mediated adverse events that occurred in at least five participants, all of which were in the pembrolizumab group, were severe skin reactions, hepatitis, and pneumonitis.

Discussion

At the protocol-specified second interim analysis of the randomised, triple-blind, placebo-controlled, phase 3 PEARLS/KEYNOTE-091 trial of stage IB (tumours of

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	358 (62%)	166 (29%)	21 (4%)	11 (2%)	379 (65%)	130 (22%)	14 (2%)	6 (1%)
Increased bodyweight	127 (22%)	6 (1%)	0	0	159 (27%)	9 (2%)	0	0
Pruritus	124 (21%)	1 (<1%)	0	0	72 (12%)	2 (<1%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Arthralgia	104 (18%)	4 (1%)	0	0	74 (13%)	1 (<1%)	0	0
Diarrhoea	99 (17%)	7 (1%)	0	0	81 (14%)	2 (<1%)	0	0
Fatigue	95 (16%)	1 (<1%)	0	0	86 (15%)	3 (1%)	0	0
Cough	86 (15%)	1 (<1%)	0	0	98 (17%)	0	0	0
Hypertension	32 (6%)	35 (6%)	0	0	42 (7%)	32 (6%)	0	0
Dyspnoea	58 (10%)	8 (1%)	0	0	65 (11%)	7 (1%)	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17 (3%)	0	0	0
Upper respiratory tract infection	53 (9%)	0	0	0	55 (9%)	0	0	0
Nausea	51 (9%)	1 (<1%)	0	0	37 (6%)	0	0	0
Nasopharyngitis	50 (9%)	0	0	0	32 (6%)	0	0	0
Rash	47 (8%)	2 (<1%)	0	0	29 (5%)	0	0	0
Increased alanine aminotransferase	42 (7%)	4 (1%)	0	0	31 (5%)	3 (1%)	0	0
Back pain	44 (8%)	1 (<1%)	0	0	46 (8%)	0	0	0
Headache	43 (7%)	2 (<1%)	0	0	45 (8%)	1 (<1%)	0	0
Asthenia	41 (7%)	3 (1%)	0	0	29 (5%)	3 (1%)	0	0
Maculopapular rash	40 (7%)	3 (1%)	0	0	20 (3%)	0	0	0
Increased aspartate aminotransferase	39 (7%)	2 (<1%)	0	0	28 (5%)	4 (1%)	0	0
Decreased appetite	40 (7%)	1 (<1%)	0	0	26 (4%)	1 (<1%)	0	0
Decreased bodyweight	39 (7%)	0	0	0	25 (4%)	0	0	0
Increased blood creatinine	38 (7%)	0	0	0	32 (6%)	0	0	0
Myalgia	35 (6%)	2 (<1%)	0	0	15 (3%)	0	0	0
Productive cough	37 (6%)	0	0	0	15 (3%)	0	0	0
Constipation	35 (6%)	0	0	0	41 (7%)	0	0	0
Influenza-like illness	34 (6%)	0	0	0	32 (6%)	0	0	0
Pneumonitis	27 (5%)	5 (1%)	2 (<1%)	0	12 (2%)	4 (1%)	0	0
Pyrexia	31 (5%)	1 (<1%)	0	0	33 (6%)	1 (<1%)	0	0
Dry skin	31 (5%)	0	0	0	21 (4%)	0	0	0
Pain in extremity	18 (3%)	0	0	0	30 (5%)	1 (<1%)	0	0
Paraesthesia	18 (3%)	0	0	0	32 (6%)	0	0	0

Data are n (%).

Table 2: **Adverse events of any cause and grade that occurred in ≥5% of participants in either treatment group in the safety population**

≥4 cm in diameter)–IIIA NSCLC (per AJCC 7th edition), we found that adjuvant pembrolizumab monotherapy significantly extended the dual primary endpoint of disease-free survival in the overall population compared with placebo after complete resection and adjuvant chemotherapy when recommended per guidelines. The significance boundary was not crossed for the other dual primary endpoint of disease-free survival in the PD-L1 TPS of 50% or greater population. A sensitivity analysis in which participants who had disease recurrence before randomisation were censored at the time of randomisation gave HRs similar to those seen in the primary analysis for both the overall population and the PD-L1 TPS of 50% or greater population. Overall survival data are immature at this interim analysis. The study is continuing as planned, and the primary endpoint of disease-free survival in the PD-L1 TPS of 50% or greater population and the secondary endpoints of disease-free survival in the PD-L1 TPS of 1% or greater population and overall survival in the overall population, PD-L1 TPS of 50% or greater population, and PD-L1 TPS of 1% or greater population will be tested at future analyses in accordance with the protocol.

The absence of a disease-free survival benefit for pembrolizumab in the PD-L1 TPS of 50% or greater population at the time of this interim analysis was unexpected because the relative benefit of pembrolizumab monotherapy increases with increasing PD-L1 expression in the setting of locally advanced or metastatic NSCLC.[17–19] As expected, median disease-free survival in the pembro-

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	180 (31%)	38 (7%)	6 (1%)	2 (<1%)	64 (11%)	11 (2%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17 (3%)	0	0	0
Pneumonitis	32 (6%)	6 (1%)	2 (<1%)	0	13 (2%)	4 (1%)	0	0
Severe skin reactions	5 (1%)	11 (2%)	0	0	2 (<1%)	2 (<1%)	0	0
Colitis	10 (2%)	4 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Adrenal insufficiency	6 (1%)	4 (1%)	0	0	0	0	0	0
Hepatitis	1 (<1%)	5 (1%)	4 (1%)	0	2 (<1%)	2 (<1%)	0	0
Hypophysitis	4 (1%)	3 (1%)	0	0	0	0	0	0
Thyroiditis	6 (1%)	0	0	0	1 (<1%)	0	0	0
Infusion reactions	5 (1%)	0	0	0	4 (1%)	0	0	0
Myocarditis	1 (<1%)	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0
Nephritis	4 (1%)	0	0	0	0	0	0	0
Pancreatitis	2 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Myositis	1 (<1%)	0	0	0	0	0	0	0
Sarcoidosis	0	1 (<1%)	0	0	0	0	0	0
Type 1 diabetes	0	1 (<1%)	0	0	0	0	0	0
Vasculitis	0	1 (<1%)	0	0	0	0	0	0

Data are n (%). Potentially immune-mediated adverse events and infusion reactions were based on a list of terms prepared by the sponsor and were considered regardless of attribution to trial treatment by the investigator. In addition to the specific preferred terms listed, related terms were included.

Table 3: **Potentially immune-mediated adverse events and infusion reactions of any incidence in the safety population**

lizumab group was numerically improved in the PD-L1 TPS of 50% or greater population compared with the PD-L1 TPS of 1–49% and less than 1% populations. Unexpectedly, median disease-free survival in the placebo group was also numerically improved in the PD-L1 TPS of 50% or greater population compared with the PD-L1 TPS of 1–49% and less than 1% populations. Because we could identify no obvious between-group imbalances in baseline characteristics, including in the distribution of the stratification factors of disease stage and receipt of adjuvant chemotherapy, random chance might have led to better-than-expected outcomes in the placebo group of the PD-L1 TPS of 50% or greater population. Although an imbalance in unknown factors (eg, molecular biomarkers) might have contributed to the outcomes, the overperformance of the placebo group probably led to the absence of significant benefit for pembrolizumab in the PD-L1 TPS of 50% or greater population. Longer follow-up will determine whether or not a significant difference in disease-free survival emerges in this population.

As reflected by the point estimates at 24 and 36 months, the difference in disease-free survival between the treatment groups is consistent over time in the overall population. Although the Kaplan-Meier curves of disease-free survival in the overall population converge at approximately 58 months, these data are unreliable because of the low number of participants at risk; long-term disease-free survival estimates will be more reliable with longer follow-up. The disease-free survival benefit of pembrolizumab in the overall population was generally consistent across protocol-specified subgroups. The statistical uncertainty of the actual treatment effect in the subgroups is reflected by the wide 95% CIs that overlapped the 95% CI of the overall treatment effect. Therefore, results of subgroup analyses, including those for which pembrolizumab appeared to have a greater effect (ie, current smokers and those with *EGFR*-mutant tumours) or lesser effect (ie, those with no previous adjuvant chemotherapy and those with squamous cell histology) than placebo on the basis of the HR, should be interpreted with caution and no definitive conclusions can be drawn. Appropriately powered randomised trials are required to determine whether the relative benefit of pembrolizumab versus placebo is truly different in these subgroups.

Our results add to the evidence base supporting immune checkpoint inhibitors as adjuvant therapy.[8,20–24] The IMpower010 study of atezolizumab enrolled a generally similar population as we did in PEARLS/KEYNOTE-091, although previous adjuvant chemotherapy was mandatory, the study had an open-label design, and the proportion of patients with stage III disease and no smoking history was higher than in our study.[8] In both IMpower010 and PEARLS/KEYNOTE-091, approximately 40% of participants had PD-L1 expression on less than 1% of tumour cells. Atezolizumab improved disease-free survival in participants with stage II–IIIA NSCLC that expressed PD-L1 on 1% or more tumour cells and in the PD-L1-unselected stage II–IIIA population, but not the overall population that included participants with stage IB (tumours of ≥4 cm in diameter) disease, and there appeared to be no benefit for atezolizumab in

participants with stage II–IIIA disease and PD-L1 expression on less than 1% of tumour cells.[8] We found that pembrolizumab significantly improved disease-free survival in the PD-L1-unselected, overall population of participants with stage IB–IIIA disease and observed generally similar benefit in the PD-L1 TPS of less than 1%, 1–49%, and 50% or greater subgroups of the overall population, supporting a benefit for pembrolizumab irrespective of PD-L1 expression. We acknowledge that the results of PEARLS/KEYNOTE-091 and IMpower010 differ. The differences in study design and enrolled populations probably had an effect. Other factors that might have contributed to the differing results include use of different assays to determine PD-L1 expression and overperformance of the PEARLS/KEYNOTE-091 placebo group in the PD-L1 TPS of 50% or greater population.

The adverse event profile observed with pembrolizumab was similar to that in previous studies of pembrolizumab monotherapy, including of locally advanced or metastatic NSCLC[17–19,25,26] and of adjuvant therapy for melanoma and renal-cell carcinoma.[20,21] As expected for a placebo-controlled trial, adverse events were more frequent in the pembrolizumab group than in the placebo group. Adverse events were manageable, with participants in the pembrolizumab group receiving a median of 17 of the planned 18 administrations. The incidence of some potentially immune-mediated adverse events, such as hypothyroidism, was higher in our study than in some studies of pembrolizumab monotherapy for advanced or metastatic NSCLC.[17–19,25,26] However, the incidence of hypothyroidism in our study (21%) was similar to that observed in a previous study of pembrolizumab as adjuvant therapy for renal-cell carcinoma (21%).[20] This increased incidence in the adjuvant setting compared with the advanced or metastatic setting is probably explained by longer pembrolizumab exposure in the adjuvant setting than in the advanced or metastatic setting.[27,28] The rate of discontinuation due to adverse events observed in this study was also higher than that observed in studies of pembrolizumab for advanced or metastatic NSCLC, probably because of longer pembrolizumab exposure in the adjuvant setting and the seemingly lower threshold for treatment discontinuation in the adjuvant setting than in the advanced or metastatic setting.[29] Two participants treated with pembrolizumab died due to myocarditis, an immune-mediated adverse event known to be associated with immune checkpoint inhibitors.[30] In one participant, myocarditis was accompanied by grade 5 septic shock. The second participant experienced septic shock 2 days before developing grade 5 myocarditis and cardiogenic shock.

Study strengths include the triple-blind, placebo-controlled design and international population. In accordance with real-world clinical practice, adjuvant chemotherapy use was not mandatory.

Limitations of our study include no requirement for *EGFR* and *ALK* testing, which precluded meaningful subgroup analysis on the basis of *EGFR* status and *ALK* status, and the absence of independent central review of baseline imaging assessments. We enrolled participants with stage IB (tumours of ≥4 cm in diameter)–IIIA NSCLC per the AJCC staging system 7th edition, which is equivalent to stage IB (tumours of 4 cm in diameter) to IIIB (tumours >7 cm in diameter, N2 nodal status) per the 8th edition currently in use. The difference in staging criteria is not expected to affect interpretation of our results. Allowing maximum intervals of 12 weeks between surgery and the start of adjuvant chemotherapy (or study treatment in those who did not receive chemotherapy) and between the last dose of adjuvant chemotherapy and the start of study treatment was done to allow time for recovery from adverse events of surgery or chemotherapy. Exploratory analyses designed to assess the association between the surgery-to-chemotherapy and chemotherapy-to-study-treatment intervals are outside the scope of this report but could be considered in the future to inform subsequent studies. Samples for biomarker assessment have been collected from consenting participants but translational analyses have not been done to date. Additional follow-up is needed to determine whether the disease-free survival benefit of pembrolizumab will result in an overall survival benefit.

In summary, pembrolizumab monotherapy provided a significant and clinically meaningful improvement in disease-free survival compared with placebo after complete resection and, when recommended per guidelines, adjuvant chemotherapy in the overall population of participants with stage IB (tumours of ≥4 cm in diameter)–IIIA NSCLC. The difference in disease-free survival in the PD-L1 TPS of 50% or greater population was not significant at this interim analysis. The safety profile observed was consistent with the known safety profile of pembrolizumab, with no new adverse events. These data suggest adjuvant pembrolizumab is potentially a new treatment option for this population, regardless of PD-L1 expression.

Contributors

MO, LP-A, SM, UD, RS, and SP contributed to the conception, design, and planning of the study. MO, LP-A, SM, UD, RS, KN, SMK, AS, BB, and SP served on the study steering committee. MO, LP-A, KO, LH, EE, DI, AM-M, MF, MT, J-SL, BB, and SP enrolled and treated participants and acquired study data. JY, MM, and NJ did statistical analyses. MO, LP-A, JY, SMK, and AS wrote the first draft of the manuscript. MO, LP-A, SM, SMK, RS, BB, and SP accessed and verified the underlying study data. All authors had access to the data, analysed and interpreted the data, provided critical review of manuscript drafts, and approved the manuscript for submission. 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.

Declaration of interests

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KO additionally reports institutional grants or contracts from Pfizer and Takeda; consulting fees from Amgen, Takeda, MSD, Janssen, Roche, and AstraZeneca; and travel support from MSD. DI additionally reports consulting fees from MSD, Roche, AstraZeneca, Amgen, Pfizer, Sanofi, Bayer, BMS, GSK, Janssen, and Takeda; honoraria from MSD, Roche, AstraZeneca, Amgen, Pfizer, Sanofi, Bayer, BMS, and Takeda; and travel support from AstraZeneca. AM-M additionally reports consulting fees for advisory board membership from AstraZeneca/MedImmune, BMS, F Hoffmann-La Roche AG, MSD, and Pfizer; honoraria from AstraZeneca/MedImmune, BMS, F Hoffmann-La Roche AG, MSD, and Pfizer; serving as a steering committee member for AstraZeneca/MedImmune; and travel support from AstraZeneca/MedImmune, BMS, F Hoffmann-La Roche AG, MSD, Pfizer, and Lilly. MF additionally reports honoraria from Roche and Sanofi; travel support from AstraZeneca; and serving as an advisory board member for MSD, Roche, and AstraZeneca. 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JY, AS, and SMK report salary for full-time employment from MSD; AS and SMK also own stock in Merck & Co, Rahway, NJ, USA.

For the **MSD data sharing website** see https://engagezone.msd.com/ds_documentation.php

Data sharing

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