Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

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Summary

Background Novel adjuvant strategies are needed to optimise outcomes after complete surgical resection in patients with early-stage non-small-cell lung cancer (NSCLC). We aimed to evaluate adjuvant atezolizumab versus best supportive care after adjuvant platinum-based chemotherapy in these patients.

Methods IMpower010 was a randomised, multicentre, open-label, phase 3 study done at 227 sites in 22 countries and regions. Eligible patients were 18 years or older with completely resected stage IB (tumours ≥4 cm) to IIIA NSCLC per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system (7th edition). Patients were randomly assigned (1:1) by a permuted-block method (block size of four) to receive adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) or best supportive care (observation and regular scans for disease recurrence) after adjuvant platinum-based chemotherapy (one to four cycles). The primary endpoint, investigator-assessed disease-free survival, was tested hierarchically first in the stage II–IIIA population subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells (SP263), then all patients in the stage II–IIIA population, and finally the intention-to-treat (ITT) population (stage IB–IIIA). Safety was evaluated in all patients who were randomly assigned and received atezolizumab or best supportive care. IMpower010 is registered with ClinicalTrials.gov, NCT02486718 (active, not recruiting).

Findings Between Oct 7, 2015, and Sept 19, 2018, 1280 patients were enrolled after complete resection. 1269 received adjuvant chemotherapy, of whom 1005 patients were eligible for randomisation to atezolizumab (n=507) or best supportive care (n=498); 495 in each group received treatment. After a median follow-up of 32·2 months (IQR 27·4–38·3) in the stage II–IIIA population, atezolizumab treatment improved disease-free survival compared with best supportive care in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells (HR 0·66; 95% CI 0·50–0·88; p=0·0039) and in all patients in the stage II–IIIA population (0·79; 0·64–0·96; p=0·020). In the ITT population, HR for disease-free survival was 0·81 (0·67–0·99; p=0·040). Atezolizumab-related grade 3 and 4 adverse events occurred in 53 (11%) of 495 patients and grade 5 events in four patients (1%).

Interpretation IMpower010 showed a disease-free survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC, with pronounced benefit in the subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells, and no new safety signals. Atezolizumab after adjuvant chemotherapy offers a promising treatment option for patients with resected early-stage NSCLC.

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Introduction

Among patients diagnosed with non-small-cell lung cancer (NSCLC), approximately 50% have localised (stages I and II) or locally advanced (stage III) disease.[1] Curative surgery is the treatment of choice for stages I and II and select cases of stage IIIA NSCLC.[2] However, 5-year survival rates decrease from 92% in patients with resected stage IA1 disease to 36% in patients with stage IIIA disease,[3] suggesting the presence of micrometastases in some patients at surgical resection. Adjuvant platinum-based combination chemotherapy, the current standard of care for completely resected early-stage NSCLC (stage IB [tumour ≥4 cm] to IIIA),[4,5] results in a modest 4–5% improvement in survival versus observation.[6,7] The Japan Intergroup Trial of Pemetrexed Adjuvant Chemotherapy for Completely Resected Nonsquamous Non-Small-Cell Lung Cancer trial showed that pemetrexed plus cisplatin had utility and tolerability

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See Online for appendix

Research in context

Evidence before this study

The use of adjuvant chemotherapy for resected early-stage (IB–IIIA) non-small-cell lung cancer (NSCLC) to improve long-term outcomes became standard practice in 2004, but the 5-year survival benefits were modest. Immunotherapy has changed NSCLC treatment practice in the advanced and metastatic setting; accordingly, immune checkpoint inhibitors are being investigated in early-stage NSCLC, with promising data emerging from neoadjuvant studies. The fact that several phase 3 studies of adjuvant checkpoint inhibitors are ongoing indicates enthusiasm for evaluating their efficacy in early-stage NSCLC after complete resection. We searched PubMed on April 20, 2021, using the search terms "adjuvant", "early-stage", "stage IB–III", "NSCLC", "resected", "PD-1 inhibitor", "PD-L1 inhibitor", "atezolizumab", "pembrolizumab", "durvalumab", and "nivolumab" for full manuscripts published during the past 10 years that described results of phase 3 trials of checkpoint inhibitor therapy in the adjuvant setting after complete resection of early-stage NSCLC. Full data for these studies have not yet been published. These findings were supplemented by searching ClinicalTrials.gov with the same search terms. In addition to our study, IMpower010, other phase 3 trials are ongoing in patients with surgically resected, stage IB–IIIA NSCLC: ANVIL, an ALCHEMIST trial (*EGFR*-negative or *ALK*-negative non-squamous and squamous NSCLC; 1 year of adjuvant nivolumab or observation after standard of care adjuvant chemotherapy or radiation); PEARLS (1 year of pembrolizumab *vs* supportive care after standard of care adjuvant therapy); and the Canadian Cancer Trials Group study BR31 (durvalumab *vs* placebo). Disease-free survival is the primary endpoint in all these studies; overall survival is a coprimary endpoint in ANVIL. MERMAID-1 (adjuvant durvalumab or placebo plus chemotherapy in stage II–IIIA, *EGFR*-wild-type or *ALK*-wild-type NSCLC) and MERMAID-2 (durvalumab *vs* placebo after neoadjuvant or adjuvant therapy in patients with stage II–III, *EGFR*-wild-type or *ALK*-wild-type NSCLC who become positive for minimal-residual disease within 96 weeks) started recruitment in the second half of 2020.

Added value of this study

To our knowledge, the data from IMpower010 are the first to emerge from the phase 3 studies of adjuvant immunotherapy in stage IB–IIIA NSCLC. Patients with completely resected stage II–IIIA NSCLC after a median four cycles of adjuvant platinum-based chemotherapy, plus up to 1 year of adjuvant atezolizumab, had significant improvements in disease-free survival compared with best supportive care, particularly in patients with tumours expressing PD-L1 on 1% or more of tumour cells. Compared with best supportive care, the risk of recurrence, new primary NSCLC, or death was reduced with atezolizumab by 34% in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, and by 21% in all patients in the stage II–IIIA population.

Implications of all the available evidence

Overall survival data were not mature at this cutoff, and longer follow-up will be needed to show a survival benefit for adjuvant atezolizumab following adjuvant chemotherapy in completely resected early-stage NSCLC. Nevertheless, the positive primary endpoint results, along with a safety profile consistent with previous reports and no new safety signals, suggest that atezolizumab after adjuvant chemotherapy might offer a promising treatment option that extends disease-free survival in patients with stage II–IIIA resected early-stage NSCLC, specifically in patients whose tumours express PD-L1 on 1% or more of their tumour cells and especially in patients whose tumours express PD-L1 on 50% or more of tumour cells.

as an adjuvant regimen, but it was not superior to vinorelbine plus cisplatin in this setting.[8] In the E1505 trial,[9] adding bevacizumab to adjuvant cisplatin-based chemotherapy did not improve disease-free survival nor the primary endpoint of overall survival.

The ADAURA trial showed a disease-free survival benefit with osimertinib in patients with resectable tumours harbouring *EGFR* mutations.[10] However, for most patients with early-stage NSCLC who have *EGFR* wild-type tumours, there remains a pressing unmet need for novel adjuvant strategies that will extend patients' survival after complete surgical resection beyond the modest benefit offered by adjuvant chemotherapy. Immune checkpoint blockade inhibition has revolutionised the treatment of unresectable locally advanced or metastatic NSCLC, with several inhibitors of the PD-L1 and PD-1 pathway currently approved for the treatment of advanced NSCLC.[4,11,12] These agents have shown efficacy and tolerability as monotherapy and in combination with chemotherapy across treatment lines, with some phase 3 trials showing an association between increasing PD-L1 expression and treatment benefit.[13–19]

The PD-L1 inhibitor atezolizumab has shown clinical benefit and a tolerable safety profile in metastatic NSCLC and has been approved for use as first-line and second-line or later treatment in this setting.[19–22] Based on these positive outcomes, there is increasing interest in the use of this agent to treat early-stage NSCLC. In this randomised, open-label, phase 3 IMpower010 trial, we aimed to evaluate adjuvant atezolizumab versus best supportive care after cisplatin-based adjuvant chemotherapy in patients with completely resected stage IB–IIIA NSCLC. Here we report primary efficacy and safety data from the pre-planned interim analysis of IMpower010.

Methods

Study design and participants

IMpower010 is a randomised, multicentre, open-label, phase 3 study of atezolizumab versus best supportive care after adjuvant cisplatin-based chemotherapy in

patients with completely resected stage IB–IIIA NSCLC, done at 227 sites in 22 countries and regions.

The study was done in two phases: enrolment and randomisation. The study protocol and full eligibility criteria can be found in the appendix (pp 20–343). The protocol was approved by an institutional review board or an independent ethics committee at each participating site.

Briefly, eligible patients were 18 years or older, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had completely resected stage IB (tumours ≥4 cm) to IIIA (T2–3 N0, T1–3 N1, T1–3 N2, and T4 N0–1 NSCLC, per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system, 7th edition),[23] and were able to receive cisplatin-based chemotherapy. Patients whose tumours were positive for *EGFR* or *ALK* alterations could enrol. Complete resection (lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy) of NSCLC with negative margins, done 28–84 days before enrolment, was required. Additionally, mediastinal lymph node dissection at specified levels (levels 7 and 4 for right-sided tumours, or levels 7 and 5 or 6 for left-sided tumours) or sampling had to be done where required (appendix p 217). A representative formalin-fixed paraffin-embedded resected tumour specimen was also required.

The second phase, randomised evaluation of atezolizumab versus best supportive care, started after completion of cisplatin-based chemotherapy (one to four cycles) in patients without disease recurrence who were still eligible. All patients provided written informed consent to participate.

Randomisation and masking

Study investigators identified and enrolled patients into the trial. 3–8 weeks after the last dose of adjuvant chemotherapy, patients were randomly assigned (1:1) by a permuted-block method with a block size of four to either the atezolizumab arm or best supportive care arm with an interactive voice-web response system. Randomisation was stratified by sex (female *vs* male), tumour histology (squamous *vs* non-squamous), extent of disease (stage IB *vs* stage II *vs* stage IIIA), and PD-L1 expression status (tumour cell [TC] 2/3 and any tumour-infiltrating immune cells [IC] *vs* TC0/1 and IC2/3 *vs* TC0/1 and IC0/1 with the SP142 immunohistochemistry assay). Masking was not done as the study had an open-label design.

Procedures

Patients entered the enrolment phase 28–84 days after complete resections of their NSCLC, and eligible patients received the investigator's choice of one of four adjuvant cisplatin-based chemotherapy regimens for up to four 21-day cycles: cisplatin 75 mg/m² intravenously on day 1 of each cycle plus either vinorelbine 30 mg/m² intravenously on days 1 and 8, docetaxel 75 mg/m² intravenously on day 1, gemcitabine 1250 mg/m² intravenously on days 1 and 8, or, in the case of patients with non-squamous NSCLC, pemetrexed 500 mg/m² intravenously on day 1.

After randomisation, patients received either 1200 mg atezolizumab intravenously on day 1 of each 21-day cycle for up to 16 cycles (or 1 year), or best supportive care. Best supportive care included observation and regular scans for disease recurrence. No crossover from best supportive care to atezolizumab was allowed.

EGFR mutation and *ALK* rearrangement status were assessed locally or centrally in patients with non-squamous NSCLC; central testing was not required for patients with squamous NSCLC. Brain imaging was required for all patients at screening and during the study to rule out CNS metastasis. Tumours were assessed with CT of the chest and upper abdomen in all patients at baseline, and every 4 months in the first year and every 6 months in the second year. Patients without disease recurrence continued disease status assessments with alternating chest CT and x-ray every 6 months during years 3–5, and annually by x-ray thereafter.

Tumour specimens were analysed at screening for PD-L1 expression with the SP142 immunohistochemistry assay (Ventana Medical Systems; Tucson, AZ, USA).[24] On the basis of emerging biomarker data and the evolving PD-L1 diagnostic testing landscape, the protocol was subsequently amended so that the primary efficacy endpoint was assessed in the population with tumours expressing PD-L1 on 1% or more of tumour cells, defined with the SP263 immunohistochemistry assay (Ventana Medical Systems).[25]

Outcomes

Investigator-assessed disease-free survival was the primary endpoint and was evaluated in the subpopulation of patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells by the SP263 immunohistochemistry assay, in all patients in the stage II–IIIA population, and in the intention-to-treat (ITT) population, defined as all patients randomly assigned in the stage IB–IIIA population.

Secondary efficacy endpoints were overall survival in the ITT population; disease-free survival in the patients in the stage II–IIIA population whose tumours expressed PD-L1 on 50% or more of tumour cells per the SP263 assay; and 3-year and 5-year disease-free survival rates in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, in all patients in the stage II–IIIA population, and in the ITT population. Prespecified exploratory subgroup analyses of disease-free survival and overall survival included baseline demographics (eg, age, sex, and race and ethnicity) and baseline prognostic characteristics (eg, tumour stage, PD-L1 expression, chemotherapy regimen before randomisation, histology, smoking history, and ECOG performance status).

All adverse events were recorded during both study phases and for 30 days (90 days for serious and immune-mediated adverse events, with no time limit for events related to study treatment) after the last dose of study treatment (atezolizumab) or the last study assessment (best supportive care) or until the initiation of another anticancer therapy, whichever occurred first.

Statistical analysis

IMpower010 was designed to enrol 1005 patients to evaluate the primary endpoint, investigator-assessed disease-free survival. Randomisation was stratified on the basis of PD-L1 expression per the SP142 assay throughout the study. Up to June 29, 2016, the protocol included disease-free survival analysis in patients irrespective of PD-L1 expression and in the PD-L1 subpopulation defined as TC2/3 or IC2/3 by SP142 in the stage II–IIIA population. In a protocol amendment on Feb 11, 2020, almost 1 year before this interim analysis was done and after all patients had been randomly assigned, the PD-L1 subpopulation to be analysed for disease-free survival was amended to patients whose tumours expressed PD-L1 on 1% or more of tumour cells as defined by the SP263 assay in the stage II–IIIA population (appendix p 342).

The primary endpoint of investigator-assessed disease-free survival and the secondary endpoint of overall survival were tested hierarchically to control the overall type I error rate at a two-sided significance level of 0·05: first disease-free survival in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, then disease-free survival in all patients in the stage II–IIIA population, then disease-free survival in the ITT population, and finally overall survival in the ITT population (appendix p 10). The trial had 90% power for the primary analysis of disease-free survival in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells, with a hazard ratio (HR) for disease recurrence or death of 0·65 (corresponding to median disease-free survival durations of 52 months in the atezolizumab group and 34 months in the best supportive care group). The trial had 91% power for the primary analysis of disease-free survival in all patients in the stage II–IIIA population, with an HR for disease recurrence or death of 0·73 (corresponding to median disease-free survival durations of 46·6 months in the atezolizumab group and 34 months in the best supportive care group). The trial had 76% power for the primary analysis of disease-free survival in the ITT population, with an HR for disease recurrence or death of 0·78 (corresponding to median disease-free survival durations of 48·7 months in the atezolizumab group and 38 months in the best supportive care group). Full details of the statistical analysis plan are provided in the protocol (appendix pp 277–286).

Disease-free survival was defined as the time from randomisation to the date of first NSCLC recurrence, occurrence of new primary NSCLC, or death from any cause, whichever occurred first. Data for patients who did not have any disease-free survival events were censored at the date of the last tumour assessment. If no post-baseline data were available, disease-free survival was censored at the date of randomisation. If recurrence of disease or new primary NSCLC before randomisation was documented, disease-free survival was censored at randomisation. The interim disease-free survival analysis was planned when approximately 190 disease-free survival events had occurred in the subpopulation of the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells.

HRs for disease-free survival were estimated by a Cox regression model, including two-sided 95% CIs. Treatment comparisons were based on the stratified log-rank test. Median disease-free survival and 3-year and 5-year landmark disease-free survival rates were estimated by Kaplan-Meier methodology, and the Brookmeyer-Crowley method and Greenwood's formula were used to establish their respective 95% CIs. Prespecified subgroup analyses to assess the consistency of the treatment effect on disease-free survival were done with unstratified HRs estimated from a Cox proportional-hazards model. Safety was analysed in the safety population, defined as all patients randomly assigned who received atezolizumab or best supportive care. Statistical analyses were completed with SAS version 9.4.

The study was done in accordance with the guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. An independent data monitoring committee periodically reviewed the safety data. This study is registered with ClinicalTrials.gov, NCT02486718.

Role of the funding source

F Hoffmann-La Roche and Genentech sponsored the study, provided the study drugs, and collaborated with the study investigators on the study design and the collection, analysis, and interpretation of the data. All authors contributed to drafting the manuscript with editorial and writing assistance funded by the sponsor, had access to all the data in the study, provided final approval to publish, and agreed to be accountable for all aspects of the manuscript.

Results

Between Oct 7, 2015, and Sept 19, 2018, 1280 patients were enrolled following complete resection with negative margins, including a protocol-specified mediastinal lymph node evaluation, and 1269 of these patients received adjuvant chemotherapy (figure 1). During the enrolment phase, 472 patients received cisplatin plus pemetrexed, 406 received cisplatin plus vinorelbine, 205 received cisplatin plus gemcitabine, and 186 received cisplatin plus docetaxel. The median number of adjuvant chemotherapy cycles received was four (range,

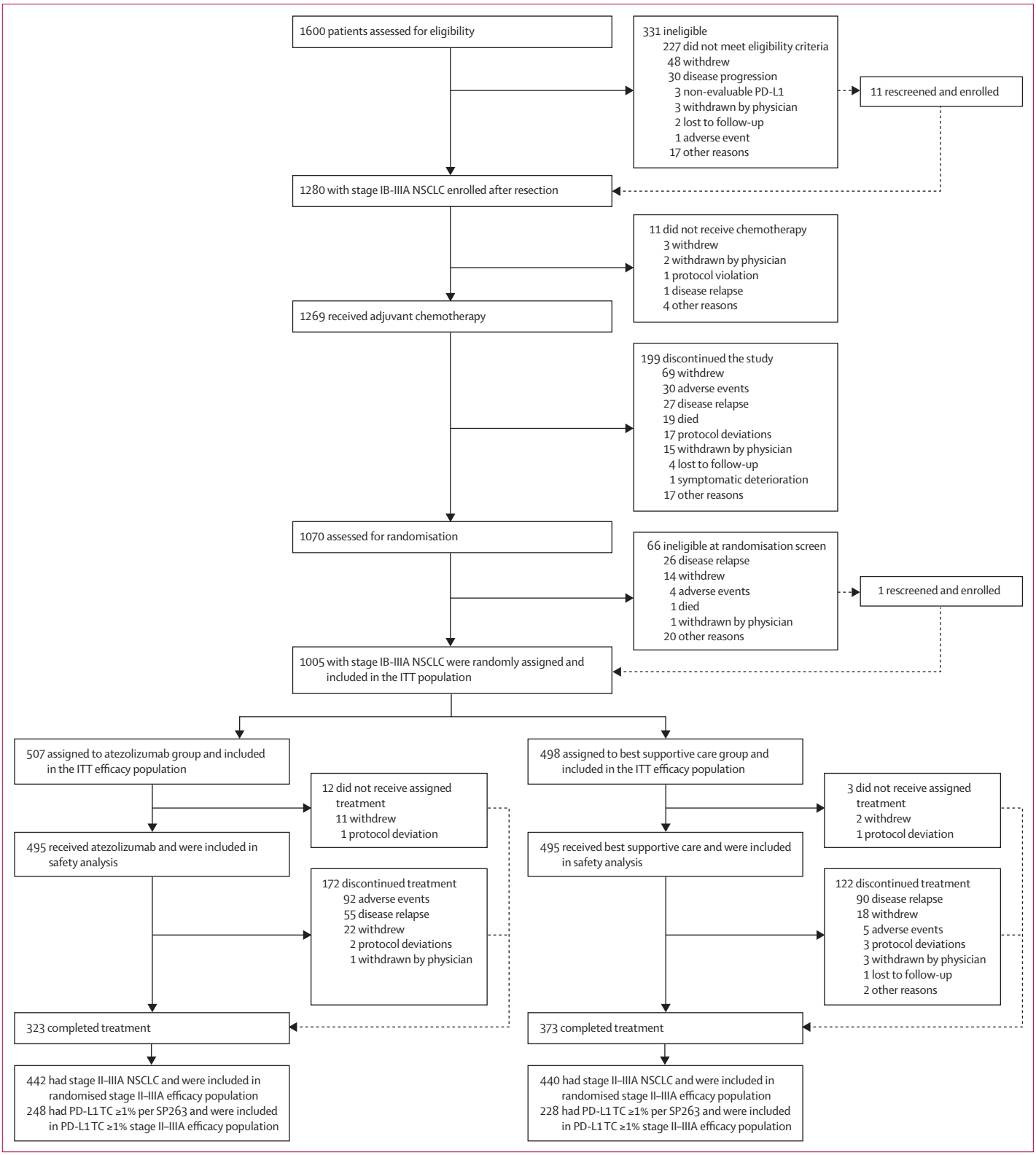


Figure 1: **Trial profile**
ITT=intention-to-treat. NSCLC=non-small-cell lung cancer. TC=tumour cells.

one to four; appendix p 13). In the randomisation phase, 507 patients were assigned to receive atezolizumab and 498 were assigned to receive best supportive care, making up the ITT population; 882 patients who were randomly assigned had stage II–IIIA disease, and of these, 476 had tumours expressing PD-L1 on 1% or more of tumour cells per SP263; these groups formed the three primary efficacy populations. Tissue for SP263 testing was available for 979 patients (97%). Baseline characteristics were generally balanced between treatment groups (table 1).

At the data cutoff (Jan 21, 2021), the median duration of follow-up for the disease-free survival analysis was 32·8 months (IQR 27·6–39·0) in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells (SP263), 32·2 months (27·4–38·3) in all patients in the stage II–IIIA population, and 32·2 months (27·5–38·4) in the ITT population.

In patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, 88 (35%) of 248 patients in the atezolizumab group and 105 (46%) of 228 patients in the best supportive care group had disease-free survival events; the stratified HR for disease-free survival was 0·66 (95% CI 0·50–0·88; p=0·0039; figure 2A). In all patients

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
Age, years	61 (56–67)	62 (56–68)	62 (56–67)	62 (55–68)	62 (57–67)	62 (56–68)
Age group						
<65 years	156 (63%)	131 (57%)	281 (64%)	263 (60%)	323 (64%)	300 (60%)
≥65 years	92 (37%)	97 (43%)	161 (36%)	177 (40%)	184 (36%)	198 (40%)
Sex						
Male	171 (69%)	147 (64%)	295 (67%)	294 (67%)	337 (66%)	335 (67%)
Female	77 (31%)	81 (36%)	147 (33%)	146 (33%)	170 (34%)	164 (33%)
Race						
White	162 (65%)	166 (73%)	307 (69%)	324 (74%)	362 (71%)	376 (76%)
Asian	78 (31%)	56 (25%)	121 (27%)	106 (24%)	130 (26%)	112 (23%)
Black or African American	2 (<1%)	0	4 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Multiple	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Unknown	5 (2%)	4 (2%)	9 (2%)	7 (2%)	9 (2%)	7 (1%)
ECOG performance status*						
0	140 (56%)	125 (55%)	239 (54%)	252 (57%)	273 (54%)	283 (57%)
1	107 (43%)	102 (45%)	201 (45%)	187 (43%)	232 (46%)	214 (43%)
2	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Histology						
Squamous	96 (39%)	85 (37%)	150 (34%)	144 (33%)	179 (35%)	167 (34%)
Non-squamous	152 (61%)	143 (63%)	292 (66%)	296 (67%)	328 (65%)	331 (67%)
Tobacco use history						
Never	51 (21%)	41 (18%)	100 (23%)	96 (22%)	114 (23%)	108 (22%)
Previous	163 (66%)	146 (64%)	277 (63%)	270 (61%)	317 (63%)	304 (61%)
Current	34 (14%)	41 (18%)	65 (15%)	74 (17%)	76 (15%)	86 (17%)
Stage						
IB	..	..	..	..	65 (13%)	58 (12%)
IIA	85 (34%)	76 (33%)	147 (33%)	148 (34%)	147 (29%)	148 (30%)
IIB	46 (19%)	37 (16%)	90 (20%)	84 (19%)	90 (18%)	84 (17%)
IIIA	117 (47%)	115 (50%)	205 (46%)	208 (47%)	205 (40%)	208 (42%)
Type of surgery						
Lobectomy	186 (75%)	173 (76%)	335 (76%)	340 (77%)	394 (78%)	391 (79%)
Sleeve lobectomy	3 (1%)	3 (1%)	4 (1%)	4 (<1%)	4 (<1%)	4 (<1%)
Bilobectomy	15 (6%)	9 (4%)	30 (7%)	17 (4%)	31 (6%)	19 (4%)
Pneumonectomy	43 (17%)	42 (18%)	72 (16%)	78 (18%)	77 (15%)	83 (17%)
Other	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

(Table 1 continues on next page)

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
(Continued from previous page)						
EGFR mutation status†						
Yes	23 (9%)	20 (9%)	49 (11%)	60 (14%)	53 (10%)	64 (13%)
No	123 (50%)	125 (55%)	229 (52%)	234 (53%)	261 (52%)	266 (53%)
Unknown	102 (41%)	83 (36%)	164 (37%)	146 (33%)	193 (38%)	168 (34%)
ALK rearrangement status†						
Yes	12 (5%)	11 (5%)	14 (3%)	17 (4%)	15 (3%)	18 (4%)
No	133 (54%)	121 (53%)	251 (57%)	256 (58%)	280 (55%)	294 (59%)
Unknown	103 (42%)	96 (42%)	177 (40%)	167 (38%)	212 (42%)	186 (37%)
PD-L1 status by SP263‡						
<1%	..	..	181 (41%)	202 (46%)	210 (41%)	234 (47%)
≥1%	248 (100%)	228 (100%)	248 (56%)	228 (52%)	283 (56%)	252 (51%)
PD-L1 status by SP142§						
TC0/1 and IC0/1	77 (31%)	66 (29%)	198 (45%)	198 (45%)	231 (46%)	231 (46%)
TC0/1 and IC2/3	66 (27%)	61 (27%)	127 (29%)	132 (30%)	146 (29%)	145 (29%)
TC2/3 and any IC	105 (42%)	101 (44%)	117 (26%)	110 (25%)	130 (26%)	122 (25%)

Data are median (IQR) or n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. IC=tumour-infiltrating immune cells. NSCLC=non-small-cell lung cancer. TC=tumour cells. *At randomisation; patients with ECOG performance status 2 had protocol deviations. †Assessed locally or centrally for patients with non-squamous NSCLC. 89% of patients with unknown *EGFR* status and 81% of patients with unknown *ALK* status in the intention-to-treat population had squamous NSCLC and were not required to undergo local or central testing. ‡26 patients in the intention-to-treat population (14 in the atezolizumab group and 12 in the best supportive care group) had unknown PD-L1 status as assessed by SP263. Of these, 23 patients (13 in the atezolizumab group and ten in the best supportive care group) had stage II–IIIA disease and were included in the stage II–IIIA population. §PD-L1 expression on TC or IC was scored as: TC0/1 and IC0/1 was <5% TC and IC; TC0/1 and IC2/3 was <5% TC and ≥5% IC; TC2/3 and any IC was ≥5% TC and any IC status.

Table 1: **Baseline characteristics**

in the stage II–IIIA population, 173 (39%) of 442 patients receiving atezolizumab and 198 (45%) of 440 receiving best supportive care had disease-free survival events, and the HR for disease-free survival was 0·79 (0·64–0·96; p=0·020; figure 2B). In the ITT population, 187 (37%) of 507 patients receiving atezolizumab and 212 (43%) of 498 receiving best supportive care had disease-free survival events. In the ITT population, which comprised patients with stage IB–IIIA disease, the boundary for statistical significance for disease-free survival was not crossed (appendix p 284), with an HR of 0·81 (0·67–0·99; p=0·040; figure 2C).

In patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, the 3-year disease-free survival rates were 60% in the atezolizumab group and 48% in the best supportive care group. In all patients in the stage II–IIIA population, the 3-year disease-free survival rates were 56% in the atezolizumab group and 49% in the best supportive care group, and in the ITT population, they were 58% in the atezolizumab group and 53% in the best supportive care group. The 5-year disease-free survival rates were not estimable in either treatment group in any study population at this interim analysis.

For the secondary endpoint of disease-free survival in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 50% or more of tumour cells, the unstratified HR was 0·43 (95% CI 0·27–0·68; figure 3B). In post-hoc exploratory analyses, in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1–49% of tumour cells, the unstratified HR was 0·87 (0·60–1·26). In patients in the stage II–IIIA population whose tumours expressed PD-L1 on less than 1% of tumour cells, the unstratified HR was 0·97 (0·72–1·31). A disease-free survival benefit in favour of atezolizumab versus best supportive care was generally seen across most patient subgroups in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells (figure 3A) and the stage II–IIIA population (figure 3B), although these exploratory analyses should be interpreted with caution.

Overall survival was not formally tested according to the statistical hierarchy, because statistical significance for disease-free survival was not met in the ITT population and the overall survival data were immature, with only 187 (19%) of 1005 death events having occurred in the ITT population at the cutoff date: 97 patients (19%) in the atezolizumab group and 90 patients (18%) in the best supportive care group. The stratified HR was 1·07 (95% CI 0·80–1·42) in the ITT population, 0·99 (0·73–1·33) in all patients in the stage II–IIIA population, and 0·77 (0·51–1·17) in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells (appendix pp 11–12).

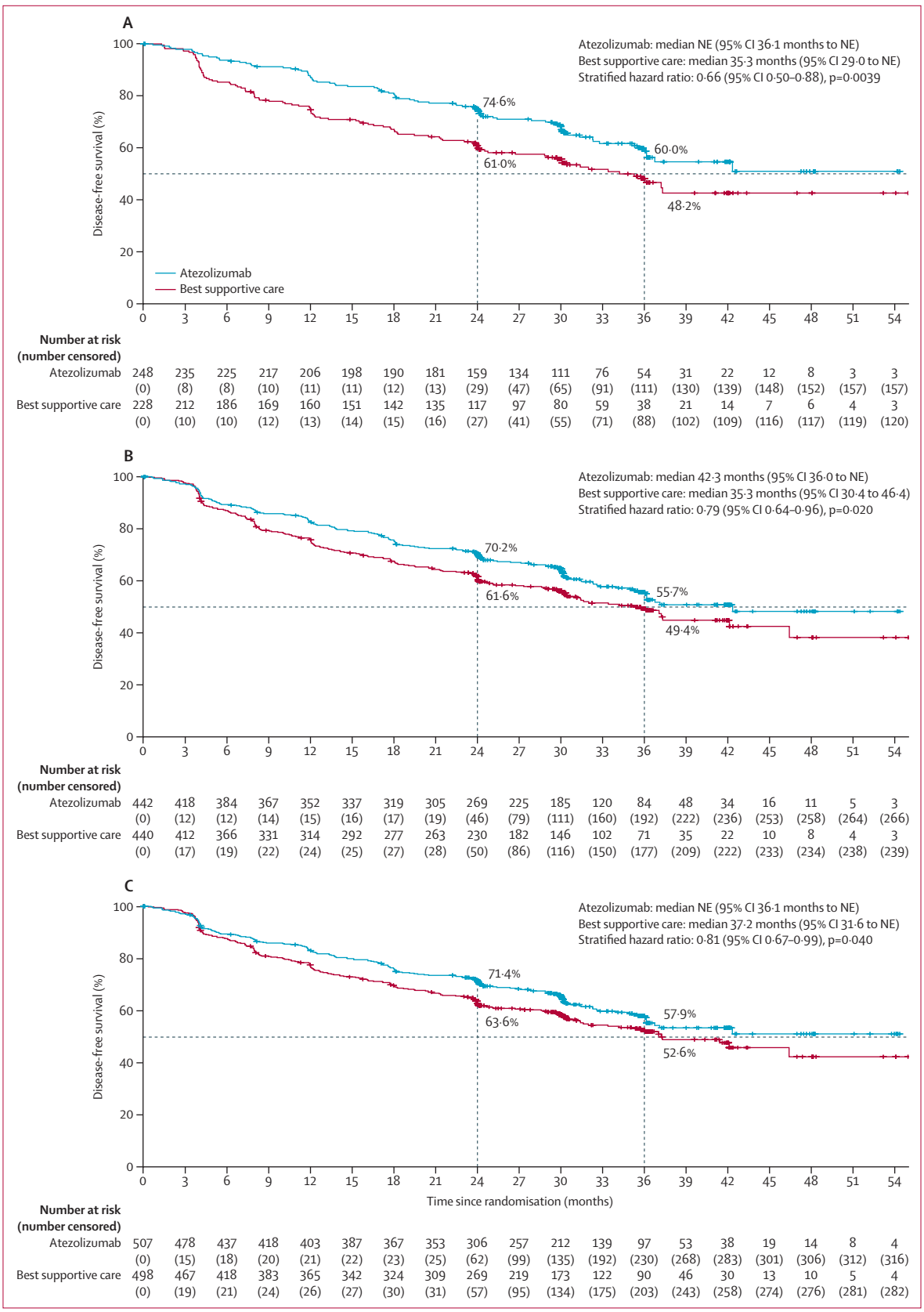
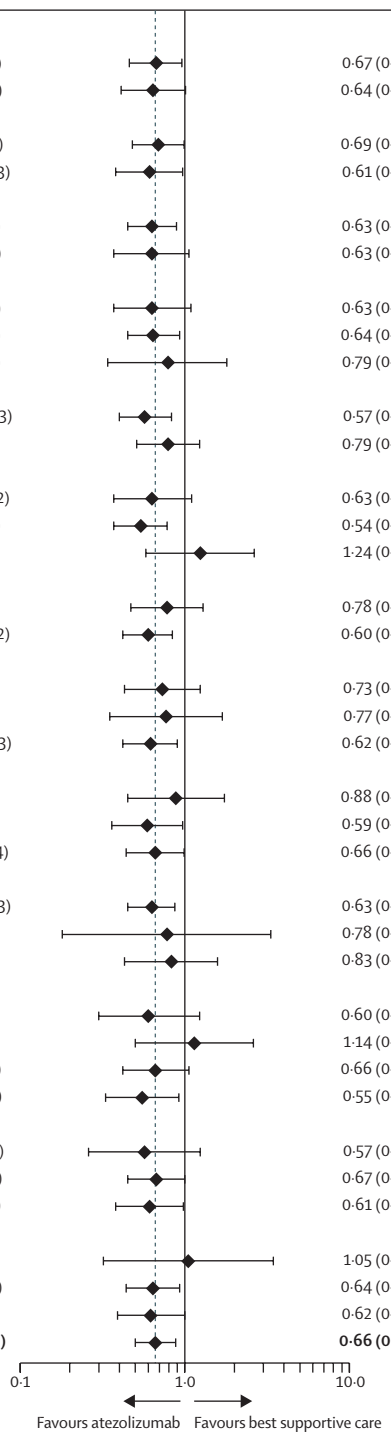


***Figure 2*: Disease-free survival in the atezolizumab and best supportive care groups**
Kaplan-Meier estimates of disease-free survival are shown for patients whose tumours expressed PD-L1 on 1% or more of tumour cells (per the SP263 assay) in the stage II–IIIA population (A), all patients in the stage II–IIIA population (B), and the intention-to-treat population (C).

A

	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
Age					
<65 years	156/287	NE (36·0–NE)	131/287	34·2 (29·7–NE)	0·67 (0·46–0·96)
≥65 years	92/189	42·3 (32·3–NE)	97/189	36·0 (23·0–NE)	0·64 (0·41–1·01)
Sex					
Male	171/318	NE (36·7–NE)	147/318	36·0 (29·0–NE)	0·69 (0·48–0·99)
Female	77/158	NE (31·3–NE)	81/158	30·1 (23·9–37·3)	0·61 (0·38–0·97)
Race					
White	162/328	NE (36·1–NE)	166/328	35·3 (29·7–NE)	0·63 (0·45–0·89)
Asian	78/134	42·3 (30·5–NE)	56/134	31·4 (18·0–NE)	0·63 (0·37–1·06)
Region					
Asia-Pacific	75/129	42·3 (30·5–NE)	54/129	31·4 (18·3–NE)	0·63 (0·37–1·09)
Europe and the Middle East	145/289	NE (36·1–NE)	144/289	35·3 (29·7–NE)	0·64 (0·45–0·93)
North America	28/57	NE (24·1–NE)	29/57	35·7 (23·9–NE)	0·79 (0·34–1·80)
ECOG performance status					
0	140/265	NE (35·5–NE)	125/265	30·4 (24·0–37·3)	0·57 (0·40–0·83)
1	107/209	36·7 (36·0–NE)	102/209	NE (28·8–NE)	0·79 (0·51–1·23)
Tobacco use history					
Never	51/92	31·3 (29·4–36·1)	41/92	20·5 (12·2–37·2)	0·63 (0·37–1·10)
Previous	163/309	NE (42·3–NE)	146/309	35·3 (26·7–NE)	0·54 (0·37–0·78)
Current	34/75	36·7 (27·9–NE)	41/75	NE (34·2–NE)	1·24 (0·58–2·64)
Histology					
Squamous	96/181	NE (36·1–NE)	85/181	NE (32·0–NE)	0·78 (0·47–1·29)
Non-squamous	152/295	42·3 (35·5–NE)	143/295	30·1 (23·0–37·2)	0·60 (0·42–0·84)
Stage					
IIA	85/161	NE (36·1–NE)	76/161	NE (29·7–NE)	0·73 (0·43–1·24)
IIB	46/83	NE (35·3–NE)	37/83	NE (32·0–NE)	0·77 (0·35–1·69)
IIIA	117/232	42·3 (30·5–NE)	115/232	26·7 (18·0–35·3)	0·62 (0·42–0·90)
Regional lymph node stage (pN)					
N0	60/106	36·7 (35·5–NE)	46/106	NE (32·0–NE)	0·88 (0·45–1·74)
N1	100/194	NE (NE–NE)	94/194	NE (30·4–NE)	0·59 (0·36–0·97)
N2	88/176	32·3 (24·2–NE)	88/176	21·3 (15·7–31·4)	0·66 (0·44–0·99)
Type of surgery					
Lobectomy	186/359	NE (36·0–NE)	173/359	33·4 (26·7–37·3)	0·63 (0·45–0·87)
Bilobectomy	15/24	36·7 (36·1–NE)	9/24	NE (6·2–NE)	0·78 (0·18–3·33)
Pneumonectomy	43/85	36·1 (30·1–NE)	42/85	NE (19·4–NE)	0·83 (0·43–1·58)
Chemotherapy regimen					
Cisplatin plus docetaxel	34/71	36·1 (31·3–NE)	37/71	18·0 (8·3–NE)	0·60 (0·30–1·23)
Cisplatin plus gemcitabine	47/75	36·1 (30·1–NE)	28/75	NE (35·3–NE)	1·14 (0·50–2·61)
Cisplatin plus pemetrexed	84/169	NE (32·8–NE)	85/169	31·4 (24·5–NE)	0·66 (0·42–1·06)
Cisplatin plus vinorelbine	83/161	NE (NE–NE)	78/161	34·2 (23·9–NE)	0·55 (0·33–0·92)
***EGFR* mutation status**					
Yes	23/43	29·7 (18·0–NE)	20/43	16·6 (6·7–31·4)	0·57 (0·26–1·24)
No	123/248	NE (35·5–NE)	125/248	36·0 (26·7–NE)	0·67 (0·45–1·00)
Unknown	102/185	NE (36·1–NE)	83/185	35·3 (23·9–NE)	0·61 (0·38–0·98)
***ALK* rearrangement status**					
Yes	12/23	30·5 (17·1–NE)	11/23	37·2 (21·3–NE)	1·05 (0·32–3·45)
No	133/254	42·3 (35·5–NE)	121/254	30·4 (23·9–NE)	0·64 (0·44–0·93)
Unknown	103/199	NE (36·7–NE)	96/199	37·3 (30·1–NE)	0·62 (0·39–1·00)
All patients	**248/476**	**NE (36·1–NE)**	**228/476**	**35·3 (29·0–NE)**	**0·66 (0·50–0·88)**



(Figure 3 continues on next page)

B

	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
Age					
<65 years	281/544	NE (35·5–NE)	263/544	35·7 (30·4–46·4)	0·79 (0·61–1·03)
≥65 years	161/338	42·3 (31·3–NE)	177/338	31·0 (24·7–NE)	0·76 (0·54–1·05)
Sex					
Male	295/589	NE (36·7–NE)	294/589	36·0 (31·0–NE)	0·76 (0·59–0·99)
Female	147/293	34·9 (30·2–NE)	146/293	30·4 (25·1–37·3)	0·80 (0·57–1·13)
Race					
White	307/631	37·1 (35·3–NE)	324/631	35·7 (30·4–46·4)	0·78 (0·61–1·00)
Asian	121/227	42·3 (30·2–NE)	106/227	31·6 (23·9–NE)	0·82 (0·55–1·22)
Unknown	9/16	NE (NE–NE)	7/16	28·6 (4·5–NE)	0·27 (0·05–1·50)
Region					
Asia-Pacific	116/219	42·3 (30·2–NE)	103/219	31·6 (24·0–NE)	0·83 (0·55–1·25)
Europe and the Middle East	270/560	NE (35·3–NE)	290/560	35·3 (30·1–46·4)	0·73 (0·56–0·94)
North America	55/101	35·5 (24·1–NE)	46/101	35·7 (23·9–NE)	1·03 (0·57–1·89)
ECOG performance status					
0	239/491	NE (35·5–NE)	252/491	35·3 (29·7–42·1)	0·72 (0·55–0·95)
1	201/388	36·1 (31·4–NE)	187/388	NE (28·6–NE)	0·87 (0·64–1·18)
Tobacco use history					
Never	100/196	30·1 (24·0–32·8)	96/196	30·4 (24·0–42·1)	1·13 (0·77–1·67)
Previous	277/547	NE (42·3–NE)	270/547	32·0 (29·7–NE)	0·62 (0·47–0·81)
Current	65/139	NE (30·1–NE)	74/139	NE (34·2–NE)	1·01 (0·58–1·75)
Histology					
Squamous	150/294	NE (36·1–NE)	144/294	46·4 (33·4–NE)	0·80 (0·54–1·18)
Non-squamous	292/588	37·1 (31·4–NE)	296/588	30·4 (24·5–37·2)	0·78 (0·61–0·99)
Stage					
IIA	147/295	NE (36·7–NE)	148/295	NE (31·0–NE)	0·68 (0·46–1·00)
IIB	90/174	37·1 (32·3–NE)	84/174	46·4 (32·0–NE)	0·88 (0·54–1·42)
IIIA	205/413	32·3 (25·4–NE)	208/413	29·7 (23·7–35·3)	0·81 (0·61–1·06)
Regional lymph node stage (pN)					
N0	118/229	NE (35·5–NE)	111/229	46·4 (37·0–NE)	0·88 (0·57–1·35)
N1	170/348	NE (37·1–NE)	178/348	36·0 (30·4–NE)	0·67 (0·47–0·95)
N2	154/305	30·2 (24·0–42·3)	151/305	24·1 (18·0–31·4)	0·83 (0·61–1·13)
PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)
Type of surgery					
Lobectomy	335/675	42·3 (34·0–NE)	340/675	32·0 (29·7–37·3)	0·77 (0·61–0·97)
Bilobectomy	30/47	36·7 (36·1–NE)	17/47	NE (6·2–NE)	1·02 (0·35–2·98)
Pneumonectomy	72/150	36·1 (30·1–NE)	78/150	42·1 (23·4–NE)	0·91 (0·56–1·47)
Chemotherapy regimen					
Cisplatin plus docetaxel	59/124	36·1 (31·3–NE)	65/124	37·3 (12·0–NE)	0·72 (0·42–1·23)
Cisplatin plus gemcitabine	77/138	36·1 (30·1–NE)	61/138	46·4 (23·8–NE)	0·94 (0·56–1·57)
Cisplatin plus pemetrexed	172/349	42·3 (32·8–NE)	177/349	31·4 (26·7–NE)	0·84 (0·61–1·16)
Cisplatin plus vinorelbine	134/271	NE (36·0–NE)	137/271	37·0 (30·1–NE)	0·67 (0·46–0·99)
***EGFR* mutation status**					
Yes	49/109	24·1 (16·1–36·1)	60/109	24·0 (12·2–31·4)	0·99 (0·60–1·62)
No	229/463	NE (32·8–NE)	234/463	36·0 (30·1–NE)	0·79 (0·59–1·05)
Unknown	164/310	NE (36·1–NE)	146/310	42·1 (30·4–NE)	0·70 (0·49–1·01)
***ALK* rearrangement status**					
Yes	14/31	30·5 (17·1–NE)	17/31	37·2 (19·5–NE)	1·04 (0·38–2·90)
No	251/507	36·1 (30·2–NE)	256/507	31·4 (24·7–NE)	0·85 (0·66–1·10)
Unknown	177/344	NE (36·1–NE)	167/344	37·3 (31·0–NE)	0·66 (0·46–0·93)
All patients	**442/882**	**42·3 (36·0–NE)**	**440/882**	**35·3 (30·4–46·4)**	**0·79 (0·64–0·96)**

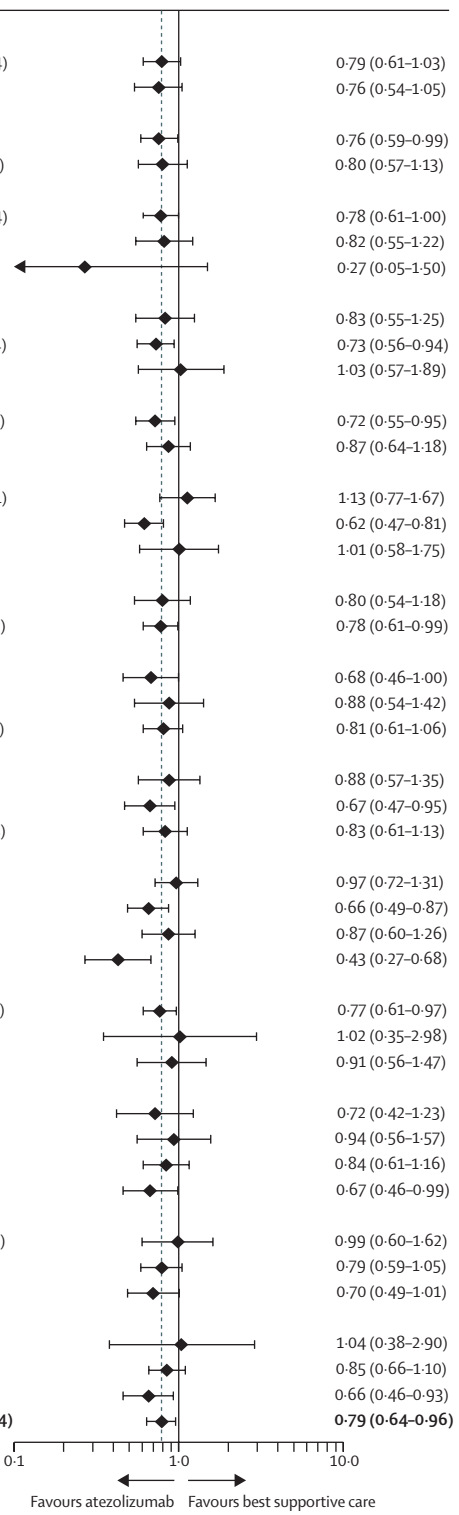


Figure 3: **DFS in key patient subgroups**
Forest plots of disease-free survival in subgroups with a total of ten or more patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells (A) and all patients in the stage II–IIIA population (B). DFS=disease-free survival. ECOG=Eastern Cooperative Oncology Group. NE=not estimable. TC=tumour cells.

57 patients (11%) in the atezolizumab group and 82 patients (16%) in the best supportive care group received subsequent radiotherapy for recurrent or new disease (postoperative radiotherapy was not permitted per the protocol; appendix p 14), 27 (5%) in the atezolizumab group and 36 (7%) in the best supportive care group had subsequent surgery, and 102 (20%) in the atezolizumab group and 131 (26%) in the best supportive care group received systemic non-protocol anticancer therapies after recurrence (appendix pp 15–16).

The safety population included 990 patients: 495 each in the atezolizumab and best supportive care groups. The median duration of atezolizumab treatment was 10·4 (IQR 4·8–10·6) months. The median number of atezolizumab cycles was 16 (IQR 7–16), with 323 patients (65%) completing 16 cycles, 125 (25%) completing zero to seven cycles, and 47 (9%) completing eight to 15 cycles.

Adverse events of any grade occurred in 459 (93%) of 495 patients receiving atezolizumab and in 350 (71%) of 495 receiving best supportive care; grade 3 or 4 events occurred in 108 patients (22%) receiving atezolizumab and 57 patients (12%) receiving best supportive care, and grade 5 events in eight patients (2%) receiving atezolizumab and three patients (1%) receiving best supportive care (table 2). Serious adverse events occurred in 87 patients (18%) in the atezolizumab group and 42 patients (8%) in the best supportive care group. The most common grade 3 or 4 adverse events in the atezolizumab group were increased alanine aminotransferase (in eight patients [2%]; table 3) and pneumonia and increased aspartate aminotransferase (each in seven [1%]). In the best supportive care group, only grade 3 or 4 pneumonia occurred in more than two patients (three patients [1%]).

Treatment-related adverse events occurred in 335 (68%) of 495 patients, and at grade 3 or 4 severity in 53 patients (11%) in the atezolizumab group. The most common atezolizumab-related adverse events were hypothyroidism in 53 patients (11%), pruritis in 43 patients (9%), and rash in 40 patients (8%; appendix p 17). Treatment-related serious adverse events occurred in 37 patients (7%) in the atezolizumab group. Grade 5 atezolizumab-related adverse events occurred in four patients (1%; myocarditis, interstitial lung disease, multiple organ dysfunction syndrome, and acute myeloid leukaemia; table 2). Atezolizumab discontinuation due to adverse events occurred in 90 patients (18%; table 2), most frequently due to pneumonitis, hypothyroidism, and increased aspartate aminotransferase (1% each).

256 patients (52%) in the atezolizumab group and 47 patients (9%) in the best supportive care group had immune-mediated adverse events (appendix p 18). These events occurred at grade 3 or 4 severity in 39 patients (8%) in the atezolizumab group and three patients (1%) in the best supportive care group. Grade 5 immune-mediated adverse events included pneumonitis and myocarditis, which each occurred in one patient (<1%) in the atezolizumab group. Immune-mediated adverse events requiring systemic corticosteroid treatment occurred in 60 patients (12%) treated with atezolizumab and in four patients (1%) who received best supportive care (appendix p 19).

	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Data are n (%). *Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

Table 2: **Safety summary in the safety evaluable population**

Discussion

The IMpower010 study met its primary endpoint of disease-free survival in patients receiving adjuvant atezolizumab versus best supportive care in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells (assessed by the SP263 assay) and in all patients in the stage II–IIIA population. The risk of recurrence, new primary NSCLC, or death with atezolizumab versus best supportive care was reduced by 34% in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells and by 21% in all patients in the stage II–IIIA population. To our knowledge, IMpower010 is the first randomised phase 3 study to show significant improvement in disease-free survival with adjuvant immunotherapy following adjuvant chemotherapy in patients with early-stage resected NSCLC. The disease-free survival benefit with atezolizumab was specifically seen in patients with tumours expressing PD-L1, particularly in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 50% or more of tumour cells. Consistent disease-free survival benefit in favour of atezolizumab was also seen in key clinical subgroups in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells and in all patients in the stage II–IIIA population. The benefit was not pronounced in patients whose tumours expressed PD-L1 on 1–49% of tumour cells, but these exploratory subgroup analyses should be interpreted with caution. Overall survival was not formally tested

	Atezolizumab group (n=495)			Best supportive care group (n=495)		
	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5
Any cause	459 (93%)	108 (22%)	8 (2%)†	350 (71%)	57 (12%)	3 (1%)‡
Cough	66 (13%)	0	0	46 (9%)	0	0
Pyrexia	65 (13%)	4 (1%)	0	11 (2%)	1 (<1%)	0
Hypothyroidism	55 (11%)	0	0	3 (1%)	0	0
Alanine aminotransferase increased	53 (11%)	8 (2%)	0	16 (3%)	1 (<1%)	0
Aspartate aminotransferase increased	53 (11%)	7 (1%)	0	16 (3%)	0	0
Arthralgia	52 (11%)	2 (<1%)	0	26 (5%)	0	0
Pruritus	51 (10%)	0	0	3 (1%)	0	0
Nasopharyngitis	33 (7%)	0	0	50 (10%)	0	0

Data are n (%). *Includes all-grade adverse events occurring in 10% or more of patients in either group, along with corresponding frequencies for grade 3–4 and grade 5 events. †Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. ‡Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient.

Table 3: **Most commonly reported adverse events in the atezolizumab or best supportive care groups***

because statistical significance for disease-free survival was not met in the ITT population (which included patients with stage IB disease) and the overall survival data were immature at this interim analysis and should, therefore, be interpreted with caution.

The rate of discontinuation before randomisation was higher than anticipated (about 20% *vs* about 10%), with patient withdrawal (31%) and disease recurrence (20%) as the most common reasons for discontinuation, and might be reflective of the adjuvant setting and the early-stage disease state. The planned 16-cycle period of atezolizumab treatment was consistent with that used in other adjuvant studies,[7,11,26,27] and nearly two-thirds (65%) of the study population received all 16 doses. No new safety signals were detected, and the toxicity profile was consistent with that previously reported with atezolizumab monotherapy.[19–22,28] Immune-mediated adverse events occurred more frequently in the patients treated with atezolizumab, which was expected as these are known risks with checkpoint inhibitors.[28] The most common immune-mediated adverse events were hepatic laboratory abnormalities, rash, and hypothyroidism. Most immune-mediated adverse events were mild grade 1 or 2 events that were manageable with treatment interruption or appropriate treatment. Immune-mediated adverse events were treated with corticosteroids in 12% of patients in the atezolizumab group, which was proportional to the overall rate of immune-mediated adverse events. Approximately half of the adverse events that led to discontinuation were grade 1–2, which might indicate that investigators had a lower threshold for discontinuing treatment in patients with early-stage NSCLC due to treatment-related toxicity than might be seen in the metastatic setting. Overall, more toxicity was observed in the atezolizumab group than in the observational best supportive care group. However, these risks should be weighed against the degree of treatment benefit, and within this context, the overall benefit–risk ratio with atezolizumab in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells appears to be favourable.

Since the landmark 2004 International Adjuvant Lung Cancer Trial study[6] showed the efficacy of adjuvant chemotherapy for NSCLC with a disease-free survival HR of 0·83 (95% CI 0·74–0·94) and an overall survival HR of 0·86 (95% CI 0·76–0·98), no improvements on this standard were achieved for more than 15 years, until findings from the ADAURA trial[10,29] of 3 years' adjuvant osimertinib treatment in patients with *EGFR*-driven NSCLC led to its being approved as adjuvant NSCLC treatment in patients whose tumours harbour *EGFR* mutations. The results from our study (IMpower010) now provide another positive outcome with adjuvant treatment in patients with resected stage II–IIIA NSCLC. All patients received chemotherapy as part of the protocol, which remains an important part of adjuvant therapy.

The IMpower010 subgroup analyses showed that in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, the disease-free survival benefit of adjuvant atezolizumab appeared to be similar in patients with *EGFR*-positive, *EGFR*-negative, and unknown status. However, these data should be interpreted with caution due to the small number of patients with a positive *EGFR* status (n=43). Most patients with unknown *EGFR* (89%) or *ALK* status (81%) had squamous NSCLC, as testing was not required in these patients.

The findings from IMpower010 also supplement positive results with other checkpoint inhibitors in adjuvant melanoma trials,[30] and support the promise of immunotherapy in the adjuvant setting. Data from other randomised phase 3 adjuvant studies of PD-L1 and PD-1 inhibitors (PEARLS,[27] BR31 [NCT02273375], ANVIL, an ALCHEMIST study,[26] MERMAID-1,[31] and MERMAID-2[32]) might further elucidate the role of these agents in the adjuvant setting in early-stage resectable NSCLC. Whether PD-L1 and PD-1 inhibitors will be safer and more effective at extending survival when used in the neoadjuvant

setting (ie, when the tumour and lymph nodes are intact—important for T-cell priming enhanced by PD-1 blockade—and when micrometastases are more likely to be eradicated) remains to be seen.[33] Phase 2 studies have shown promising efficacy and safety for neoadjuvant PD-L1 and PD-1 inhibitors in early-stage NSCLC and several phase 3 studies are ongoing.[33–35] CheckMate 816,[36] a phase 3 study of neoadjuvant nivolumab plus chemotherapy in stage IB–IIIA NSCLC, met its primary endpoint of pathological complete response in the ITT population. The results of the event-free survival endpoint for CheckMate 816 and IMpower030,[34] and other randomised studies of neoadjuvant strategies, are awaited.

Study strengths include the large global patient population, the standardisation of the adjuvant chemotherapy, and the standardised endpoints powered to show differences between treatment arms. Study limitations include the open-label design and lack of placebo control. The open-label study design was chosen for safety considerations, in the context of the standard of care at the time. Good Clinical Practice and National Comprehensive Cancer Network[4] and European Society of Medical Oncology[5] guidelines were adhered to in this study to ensure standard patient care and minimise the potential bias of the open-label design. The frequency and types of scans were consistent with those of a global trial, and the study protocol allowed for any patient to have additional scans as clinically indicated, done according to the protocol. A placebo arm was not included in the adjuvant setting to avoid placing the burden of 1 year of 3-weekly intravenous treatment visits on patients who had undergone potentially curative resection and adjuvant chemotherapy. Although the SP142 assay, which measures PD-L1 expression in both tumour-infiltrating immune cells and tumour cells, has shown predictive value for atezolizumab, it might be less sensitive on tumour cells in NSCLC than other PD-L1 assays.[15,35] Therefore, although the SP142 assay was used during screening and enrolment, in line with the changing landscape of PD-L1 testing, the SP263 PD-L1 immunohistochemistry assay was used to define the primary analysis population. As IMpower010 did not combine adjuvant immune checkpoint inhibitor therapy with chemotherapy, whether combining atezolizumab and chemotherapy might have further extended the observed clinical efficacy is unknown. Adjuvant chemotherapy might also prime the response to adjuvant immunotherapy.

In conclusion, adjuvant atezolizumab was associated with significant improvement in disease-free survival versus best supportive care after adjuvant chemotherapy in the stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells and in all patients in the stage II–IIIA population. These positive findings, along with a safety profile consistent with previous reports and no new safety signals, suggest that atezolizumab after adjuvant chemotherapy might offer a promising treatment option that extends disease-free survival in patients with resected stage II–IIIA NSCLC whose tumours express PD-L1 on 1% or more of tumour cells, and especially in those with PD-L1 expression on 50% or more of tumour cells.

Contributors

All authors had full access to all data outputs and interpreted the data. The corresponding author had final responsibility for the decision to submit for publication. MM, EB, BG, and HW conceived and designed the study. MM developed the methodology. EB and HW searched the literature. EF, MM, EB, and HW collected the data. All authors analysed and interpreted the data. FW and YD did the statistical analysis. All authors drafted and revised the manuscript. All authors critically revised the manuscript for intellectual content. NA provided administrative, technical, or material support. EF oversaw author reviews of the report. EF, NA, CZ, TC, IV, OG, AL, AA, AM-M, HK, Y-MC, AC, SS, EB, and HW selected patients. EF, NA, CZ, TC, IV, OG, AL, AA, AM-M, HK, Y-MC, AC, SS, and HW recruited and treated patients. EF and HW were part of the steering committee. All authors approved the final version of the submitted report and agree to be accountable for all aspects. All authors verify that this study was done per protocol and vouch for data accuracy and completeness.

Declaration of interests

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Data sharing

Qualified researchers can request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to

request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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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

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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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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.

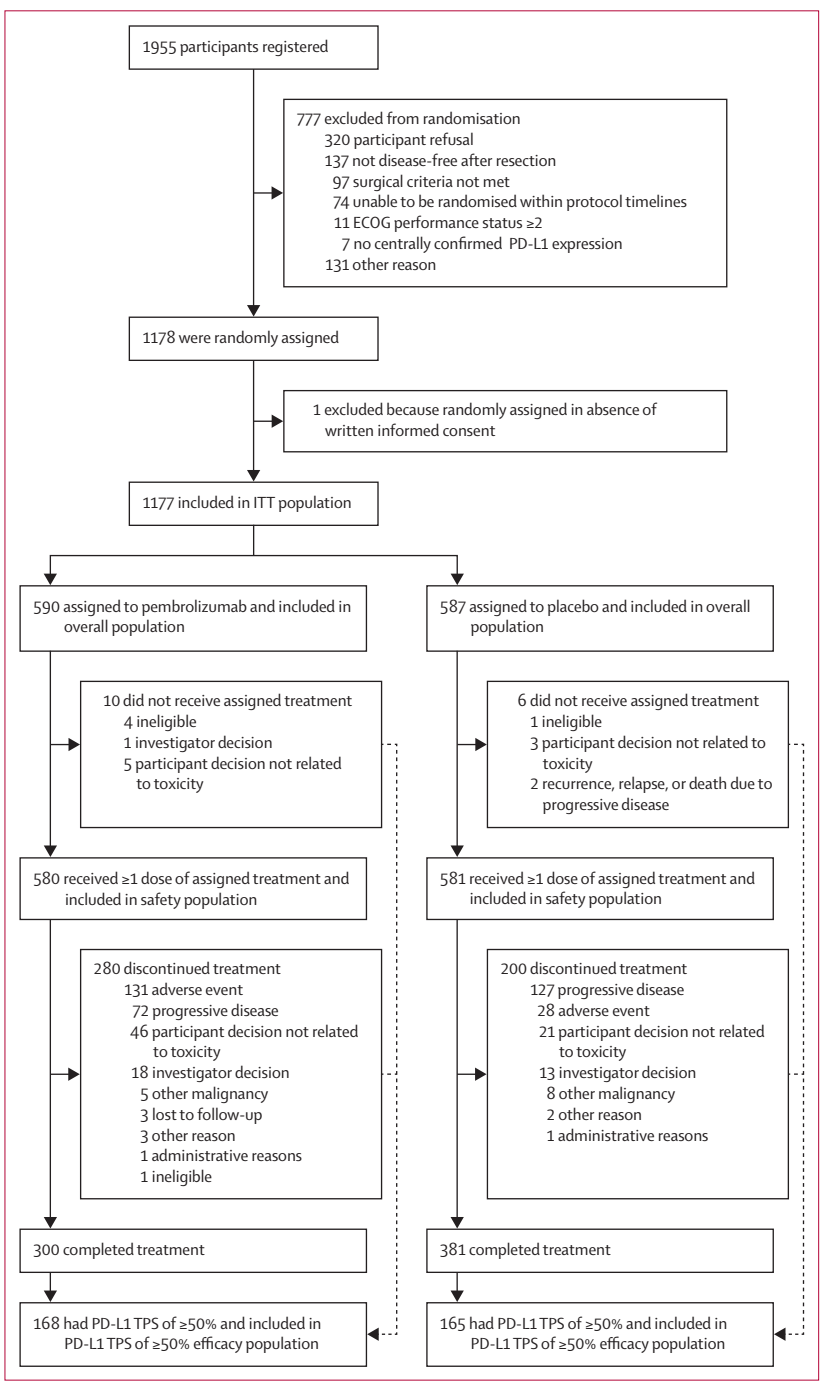

Figure 1: **Study profile**
No study data were collected for the participant excluded from the ITT population, who was randomly assigned in the absence of written informed consent. ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. PD=progressive disease. TPS=tumour proportion score.

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

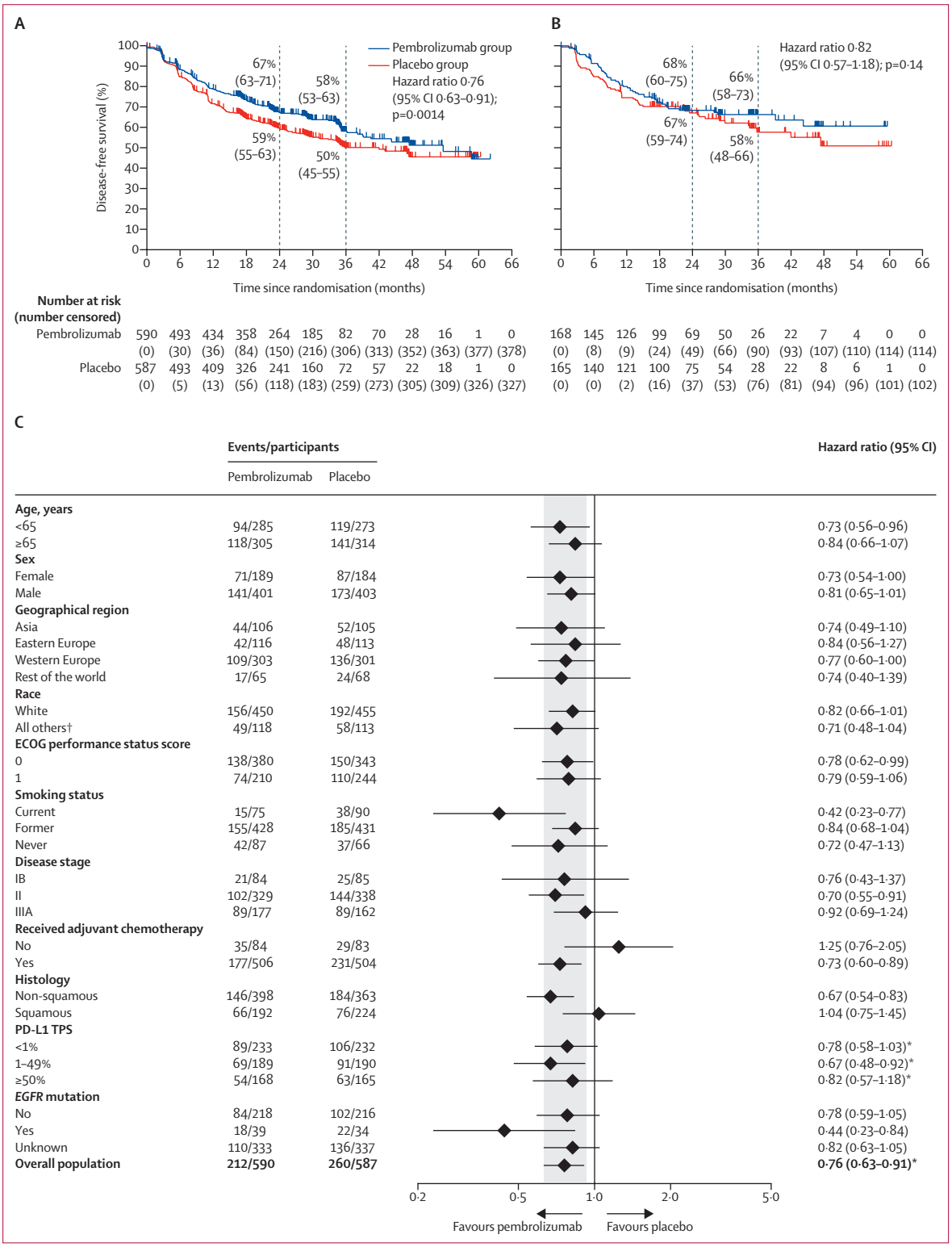

Figure 2: **Disease-free survival in the intention-to-treat population**
Kaplan-Meier estimates of disease-free survival assessed per RECIST version 1.1 by investigator review are shown for (A) the overall population and (B) the PD-L1 TPS of 50% or greater population.
(C) Disease-free survival in subgroups 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.

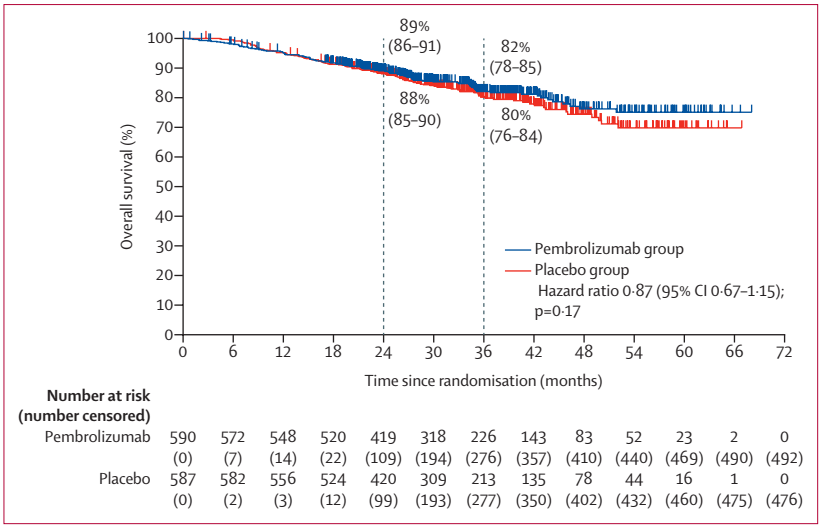

Figure 3: **Kaplan-Meier estimate of overall survival in the intention-to-treat population**
Tick marks indicate censored data.

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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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

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 outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. 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 might prevent MSD from sharing requested data, including country-specific 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 analysis portal so that the requestor can perform the proposed analyses.

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