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

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

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.

Funding F Hoffmann-La Roche and Genentech.

Published Online
September 20, 2021
https://doi.org/10.1016/S0140-6736(21)02098-5

See Online/Comment
https://doi.org/10.1016/S0140-6736(21)02100-0

*The IMpower010 Investigators are listed in the appendix

Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain (Prof E Felip MD, A Martinez-Marti MD); **Division of Thoracic Surgery, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA** (N Altorki MD); **Department of Oncology, Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China** (Prof C Zhou MD); **Jász-Nagykun-Szolnok Megyei Heténi Géza Kórház-Rendelőintézet, Szolnok, Hungary** (T Csőszi MD); **Regional Municipal Institution Sumy Regional Clinical Oncology Dispensary, Sumy State University, Sumy, Ukraine** (I Vynnychenko MD); **MI Zaporizhzhia Regional Clinical Oncological Dispensary Zaporizhzhia SMU Ch of Oncology, Zaporizhzhya, Ukraine** (O Goloborodko PhD); **Department of Thoracic Surgery, Leningrad Regional Clinical Hospital, Saint Petersburg, Russia** (A Luft MD); **Research Institute of Pulmonology, Pavlov State Medical University, Saint Petersburg, Russia** (Prof A Akopov MD); **Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan** (H Kenmotsu MD); **Department of Chest Medicine, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan** (Prof Y-M Chen MD);

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

Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy (A Chella MD); **Department of Pulmonary Medicine, Sendai Kousei Hospital, Miyagi, Japan** (S Sugawara MD); **Roche (China) Holding, Shanghai, China** (F Wu MS); **Genentech, South San Francisco, CA, USA** (D Voong MD, J Yi PhD, Y Deng PhD, M McCleland PhD, E Bennett MSHS, B Gitlitz MD); **Department of Medicine, Division of Oncology, Stanford University School of Medicine and Stanford Cancer Institute, Stanford, CA, USA** (Prof H Wakelee MD)

Correspondence to: Dr Enriqueta Felip, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona 08035, Spain
efelip@vhio.net

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,

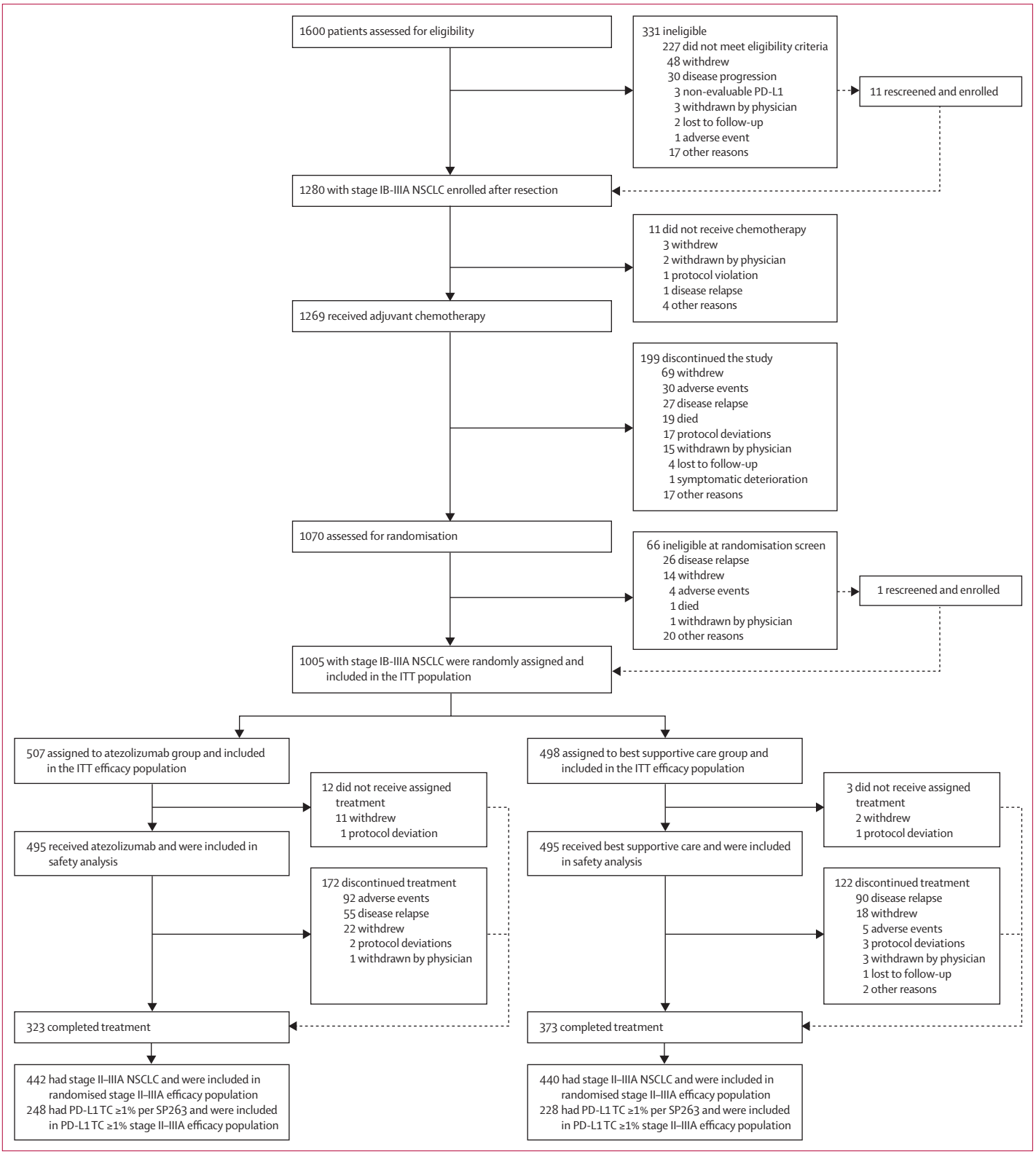


Figure 1: **Trial profile**
ITT=intention-to-treat. NSCLC=non-small-cell lung cancer. TC=tumour cells.

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).

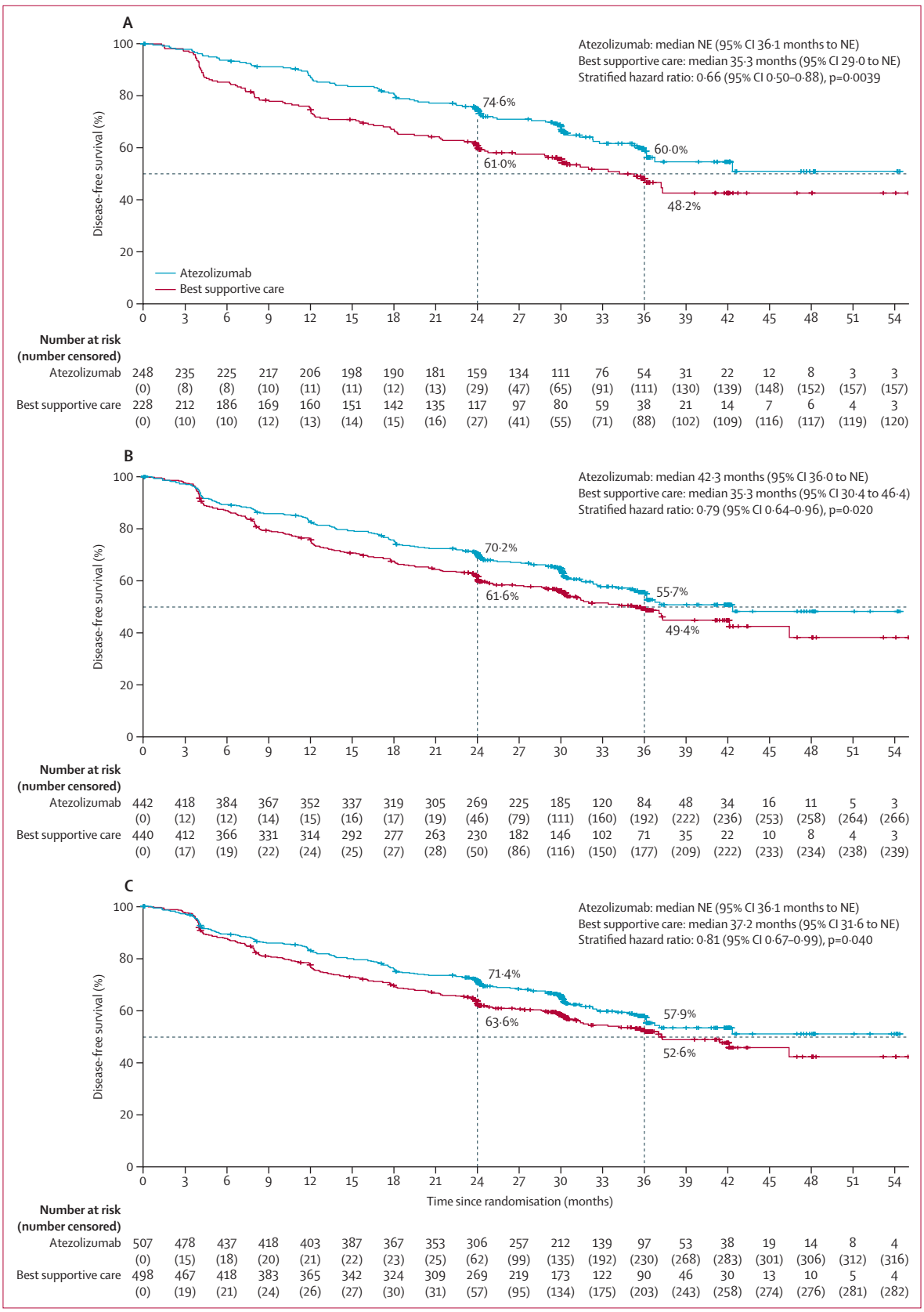
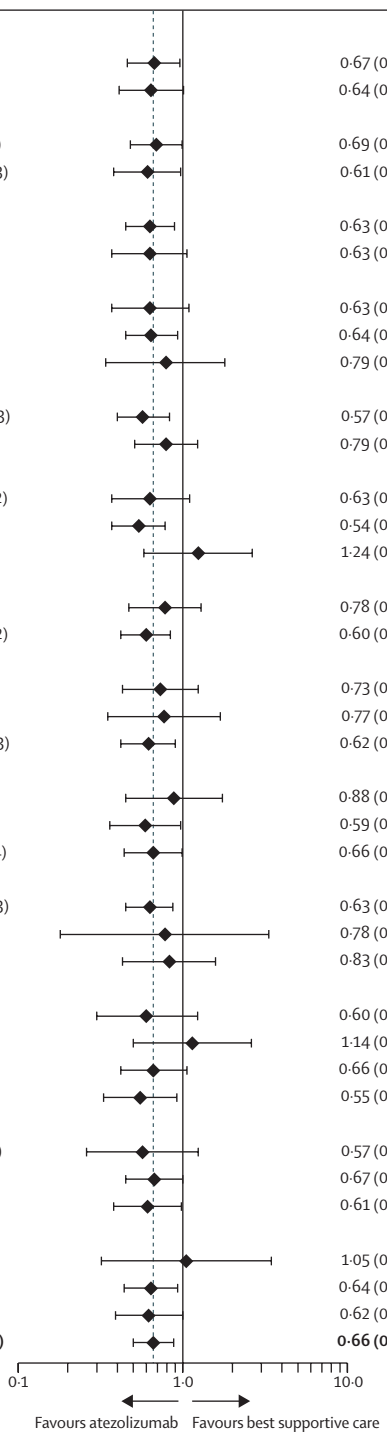


Figure 2: **Disease-free survival in the atezolizumab and best supportive care groups**
Kaplan-Meier estimates of disease-free survival are shown for patients whose tumours expressed PD-L1 on 1% or more of tumour cells (per the SP263 assay) in the stage II–IIIA population (A), all patients in the stage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

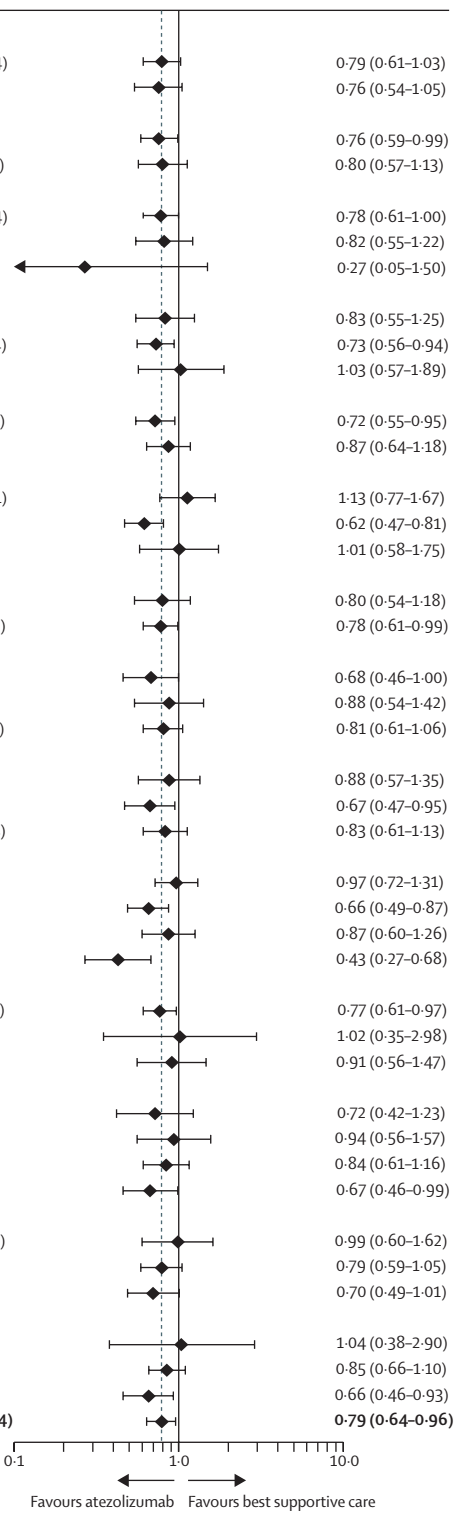


Figure 3: **DFS in key patient subgroups**
Forest plots of disease-free survival in subgroups with a total of ten or more patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells (A) and all patients in the stage II–IIIA population (B). DFS=disease-free survival. 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

All authors report editorial support from F Hoffmann-La Roche. EF received advisory or consulting fees from Amgen, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly, F Hoffman-La Roche, GlaxoSmithKline, Janssen, Medical Trends, Merck Sharp & Dohme (MSD), Merck Serono, Peptomyc, Pfizer, Puma, Regeneron, Sanofi, Syneos Health, and Takeda; received honoraria from Amgen, AstraZeneca, Bristol–Myers Squibb, Eli Lilly, F Hoffman-La Roche, Janssen, Medscape, Medical Trends, MSD, Merck Serono, Peervoice, Pfizer, Springer, and Touch Medical; and is an independent member of the board for and has received personal fees from GRIFOLS. NA received grants or contracts from AstraZeneca, the National Cancer Institute, New York Genome Center P1000 and LC200388 the US Department of Defense; and received honoraria from AstraZeneca and Regeneron. CZ received honoraria from Lilly China, Sanofi, Boehringer Ingelheim, Roche, MSD, Qilu, Hengrui, Innovent, C-Stone, LUYE Pharma, TopAlliance Bioscience, and Amoy Diagnostics; and participated in a data safety monitoring board or advisory board for Innovent Biologics, Hengrui, Qilu, and TopAlliance Bioscience. AM-M received personal fees and travel expenses from Bristol–Myers Squibb, F Hoffmann-La Roche, MSD, Pfizer, Boehringer Ingelheim, MSD Oncology, and AstraZeneca, outside the submitted work. HK received research funding from Chugai Pharmaceutical, Novartis Pharma KK, Daiichi-Sankyo, AstraZeneca KK; and received honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, Boehringer Ingelheim, Eli Lilly KK, Kyowa Hakko Kirin, Bristol–Myers Squibb, MSD, Novartis Pharma KK, Daiichi-Sankyo, AstraZeneca KK, Pfizer, and Taiho Pharma. SS received honoraria from Chugai Pharma. DV, YD, and MM are employed by Genentech. FW is employed by Roche (China). JY, EB, and BG are employed by Genentech and have stock ownership of F Hoffmann-La Roche. HW received research funding (to institution) from ACEA Biosciences, Arrys Therapeutics, AstraZeneca/Medimmune, Bristol–Myers Squibb, Celgene, Clovis Oncology, Genentech/Roche, Merck, Novartis, Pharmacyclics, SeaGen, Xcovery, and Eli Lilly; received honoraria from Novartis and AstraZeneca; received compensation for advisory boards from AstraZeneca, Xcovery, Janssen, Daiichi Sankyo, Blueprint, Mirati, and Helsinn; served in an uncompensated role for advisory boards for Merck, Takeda, Genentech/Roche, and Cellworks; and reports an uncompensated leadership role with the International Association for the Study of Lung Cancer. All other authors have no competing interests.

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).

Acknowledgments

We thank the patients participating in this trial and the clinical study site investigators and site personnel. We thank Virginia McNally of Roche Products for clinical expertise and guidance, Maureen Peterson and Patty Leon of Genentech for biomarker operations, Lei Yang, formerly of Roche (China) Holding, for statistical expertise, and Christian Hertig of F Hoffmann-La Roche for the medical data review. Medical writing assistance for this report was provided by Kia C E Walcott and Samantha Santangelo of Health Interactions, funded by F Hoffmann-La Roche.

References

1 Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res* 2019; **11:** 943–53.

2 Ghysen K, Vansteenkiste J. Immunotherapy in patients with early stage resectable nonsmall cell lung cancer. *Curr Opin Oncol* 2019; **31:** 13–17.

3 Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; **11:** 39–51.

4 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Non-small cell lung cancer version 8.2020. 2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed Nov 27, 2020).

5 Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28:** iv1–21.

6 Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; **350:** 351–60.

7 Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; **26:** 3552–59.

8 Kenmotsu H, Yamamoto N, Yamanaka T, et al. Randomized phase III study of pemetrexed plus cisplatin versus vinorelbine plus cisplatin for completely resected stage II to IIIA nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2020; **38:** 2187–96.

9 Wakelee HA, Dahlberg SE, Keller SM, et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2017; **18:** 1610–23.

10 Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. *N Engl J Med* 2020; **383:** 1711–23.

11 Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377:** 1919–29.

12 Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29:** iv192–237.

13 Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387:** 1540–50.

14 Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389:** 255–65.

15 Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 2017; **376:** 2415–26.

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

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

18 Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019; **393:** 1819–30.

19 Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med* 2020; **383:** 1328–393.

20 Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; **387:** 1837–46.

21 Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389:** 255–65.

22 Ardizzoni A, Azevedo S, Rubio-Viqueira B, et al. Primary results from TAIL: a global single-arm safety study of atezolizumab monotherapy in a diverse population of patients with previously treated advanced non-small cell lung cancer. *J Immunother Cancer* 2021; **9:** e001865.

23 Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009; **136:** 260–71.

24 Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. *Appl Immunohistochem Mol Morphol* 2019; **27:** 92–100.

25 Rebelatto MC, Midha A, Mistry A, et al. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. *Diagn Pathol* 2016; **11:** 95.

26 Chaft JE, Dahlberg SE, Khullar OV, et al. EA5142 adjuvant nivolumab in resected lung cancers (ANVIL). *J Clin Oncol* 2018; **36:** TPS8581.

27 Paz-Ares L, Hasan B, Dafni U, et al. A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (EORTC/ETOP 1416-PEARLS). *Ann Oncol* 2017; **28:** ii23.

28 Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; **36:** 1714–68.

29 Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. *J Clin Oncol* 2020; **38:** LBA5.

30 Michielin O, Atkins MB, Koon HB, Dummer R, Ascierto PA. Evolving impact of long-term survival results on metastatic melanoma treatment. *J Immunother Cancer* 2020; **8:** e000948.

31 Peters S, Spigel D, Ahn M, et al. MERMAID-1: a phase III study of adjuvant durvalumab plus chemotherapy in resected NSCLC patients with MRD+ post-surgery. *J Thorac Oncol* 2021; **16:** S258–59.

32 Spigel D, Peters S, Ahn M, et al. MERMAID-2: phase 3 study of durvalumab in patients with resected, stage II-III NSCLC who become MRD+ after curative-intent therapy. *J Thorac Oncol* 2021; **16:** S737–47.

33 Vansteenkiste J, Wauters E, Reymen B, Ackermann CJ, Peters S, De Ruysscher D. Current status of immune checkpoint inhibition in early-stage NSCLC. *Ann Oncol* 2019; **30:** 1244–53.

34 Peters S, Kim AW, Solomon B, et al. 82TiP—IMpower030: phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy. *Ann Oncol* 2019; **30:** ii30.

35 Tsao MS, Kerr KM, Kockx M, et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of blueprint phase 2 project. *J Thorac Oncol* 2018; **13:** 1302–11.

36 Forde PM, Spicer J, Lu S, et al. Nivolumab + platinum doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB IIIA) non small cell lung cancer in the phase 3 CheckMate 816 trial. American Association for Cancer Research; April 10–15, 2021 (abstr CT003).