Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial

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Summary

Background Atezolizumab (a monoclonal antibody against PD-L1), which restores anticancer immunity, improved overall survival in patients with previously treated non-small-cell lung cancer and also showed clinical benefit when combined with chemotherapy as first-line treatment of non-small-cell lung cancer. IMpower130 aimed to assess the efficacy and safety of atezolizumab plus chemotherapy versus chemotherapy alone as first-line therapy for non-squamous non-small-cell lung cancer.

Methods IMpower130 was a multicentre, randomised, open-label, phase 3 study done in 131 centres across eight countries (the USA, Canada, Belgium, France, Germany, Italy, Spain, and Israel). Eligible patients were aged 18 years or older, and had histologically or cytologically confirmed stage IV non-squamous non-small-cell lung cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and received no previous chemotherapy for stage IV disease. Patients were randomly assigned (2:1; permuted block [block size of six] with an interactive voice or web response system) to receive atezolizumab (1200 mg intravenously every 3 weeks) plus chemotherapy (carboplatin [area under the curve 6 mg/mL per min every 3 weeks] plus nab-paclitaxel [100 mg/m² intravenously every week]) or chemotherapy alone for four or six 21-day cycles followed by maintenance therapy. Stratification factors were sex, baseline liver metastases, and PD-L1 tumour expression. Co-primary endpoints were investigator-assessed progression-free survival and overall survival in the intention-to-treat wild-type (ie, *EGFR*^{wt} and *ALK*^{wt}) population. The safety population included patients who received at least one dose of the study drug. This study is registered with ClinicalTrials.gov, number NCT02367781.

Findings Between April 16, 2015, and Feb 13, 2017, 724 patients were randomly assigned and 723 were included in the intention-to-treat population (one patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population) of the atezolizumab plus chemotherapy group (483 patients in the intention-to-treat population and 451 patients in the intention-to-treat wild-type population) or the chemotherapy group (240 patients in the intention-to-treat population and 228 patients in the intention-to-treat wild-type population). Median follow-up in the intention-to-treat wild-type population was similar between groups (18·5 months [IQR 15·2–23·6] in the atezolizumab plus chemotherapy group and 19·2 months [15·4–23·0] in the chemotherapy group). In the intention-to-treat wild-type population, there were significant improvements in median overall survival (18·6 months [95% CI 16·0–21·2] in the atezolizumab plus chemotherapy group and 13·9 months [12·0–18·7] in the chemotherapy group; stratified hazard ratio [HR] 0·79 [95% CI 0·64–0·98]; p=0·033) and median progression-free survival (7·0 months [95% CI 6·2–7·3] in the atezolizumab plus chemotherapy group and 5·5 months [4·4–5·9] in the chemotherapy group; stratified HR 0·64 [95% CI 0·54–0·77]; p<0·0001]). The most common grade 3 or worse treatment-related adverse events were neutropenia (152 [32%] of 473 in the atezolizumab plus chemotherapy group *vs* 65 [28%] of 232 in the chemotherapy group), anaemia (138 [29%] *vs* 47 [20%]), and decreased neutrophil count (57 [12%] *vs* 19 [8%]). Treatment-related serious adverse events were reported in 112 (24%) of 473 patients in the atezolizumab plus chemotherapy group and 30 (13%) of 232 patients in the chemotherapy group. Treatment-related (any treatment) deaths occurred in eight (2%) of 473 patients in the atezolizumab plus chemotherapy group and one (<1%) of 232 patients in the chemotherapy group.

Interpretation IMpower130 showed a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no *ALK* or *EGFR* mutations. No new safety signals were identified. This study supports the benefit of atezolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer.

Lancet Oncol 2019

Published Online
May 20, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30167-6

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(19)30148-2

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Funding F. Hoffmann-La Roche.

Introduction

Platinum-based combination chemotherapy is the historical first-line standard of care for patients with advanced non-small-cell lung cancer, no actionable mutations, and good performance status.[1,2] For patients with non-squamous non-small-cell lung cancer and no history of haemoptysis, platinum-based chemotherapy in combination with bevacizumab is another option.[1,2] In cases of advanced non-small-cell lung cancer with sensitising mutations in *EGFR* or *ALK* alterations, European Society for Medical Oncology and National Comprehensive Cancer Network guidelines recommend treatment with tyrosine kinase inhibitors in the first instance.[1,2] Novel approaches to non-small-cell lung cancer treatment include the introduction of immunotherapies, such as anti-PD-1 and anti-PD-L1 antibodies.[1,2]

Despite the available treatments, overall survival remains low for patients with advanced non-small-cell lung cancer. Atezolizumab is an engineered, humanised monoclonal anti-PD-L1 antibody that inhibits binding of PD-L1 to PD-1 and B7.1 (also known as CD80), thus restoring anticancer immunity.[3–7] Efficacy of atezolizumab monotherapy in patients with previously treated advanced or metastatic non-small-cell lung cancer in the second-line (or beyond) setting was investigated in the phase 2 POPLAR trial (NCT01903993)[8] and phase 3 OAK trial (NCT02008227).[9] Results from both trials showed improvements in overall survival with atezolizumab versus docetaxel, with median overall survival of 12·6 months (95% CI 9·7–16·4) versus 9·7 months (8·6–12·0) in the POPLAR trial[8] and 13·8 months (11·8–15·7) versus 9·6 months (8·6–11·2) in the OAK trial.[9] Subgroup analyses suggested improvements in overall survival regardless of PD-L1 status.[8–10] On the basis of these data, atezolizumab monotherapy was approved for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer who were previously treated with chemotherapy.[6,7]

Combining atezolizumab with chemotherapy might be synergistic: chemotherapy might elicit anticancer immunity through release of potentially immunogenic tumour antigens.[11,12] Nab-paclitaxel is a nanoparticle albumin-bound form of paclitaxel that does not require steroid premedication, which has potentially immunosuppressive effects.[13] The combination of carboplatin and nab-paclitaxel is therefore an interesting chemotherapy combination to be studied with atezolizumab.

Research in context

Evidence before this study

We searched for articles and abstracts relevant to non-small-cell lung cancer and cancer immunotherapy using PubMed and various congress proceedings, including the American Society of Clinical Oncology annual meeting, the International Association for the Study of Lung Cancer World Conference on Lung Cancer, and the European Society for Medical Oncology annual meeting. We used the search terms "non-squamous NSCLC", "NSCLC", "atezolizumab", "pembrolizumab", "nivolumab", "anti-PD-L1", and "cancer immunotherapy" (full names and abbreviations), and relevant articles published from database inception to Oct 31, 2014, were selected (including clinical, non-clinical, and non-English publications). Platinum-based combination chemotherapy regimens remain the standard of care for first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer and no actionable mutations. The scientific literature searches confirmed that, despite progress with new targeted treatments—eg, for sensitising mutations in *EGFR* or *ALK* alterations, and alternative chemotherapy combinations—overall survival for advanced non-small-cell lung cancer was low and that acquired resistance to targeted agents was a major clinical problem. Therefore, alternative treatment options that yielded durable responses and enhanced overall survival were an important focus of research. Against this background, immunotherapeutic agents, such as antibodies that modulate immune cell activity, offered an alternative treatment approach that could potentially improve the prognosis of patients with this disease.

Added value of this study

Anti-PD-1 monotherapy is becoming established as a standard of care for patients with PD-L1-high, and *EGFR*-negative and *ALK*-negative tumours. The majority of patients in IMpower130 have PD-L1-low, PD-L1-negative, or PD-L1-unknown disease, and for these patients, conventional cytotoxic chemotherapy is still required in combination with immunotherapy. The results from IMpower130 suggest that atezolizumab plus chemotherapy is an additional first-line treatment option to be considered when formulating treatment plans for patients with advanced non-squamous non-small-cell lung cancer.

Implications of all the available evidence

The findings from IMpower130 suggest that addition of atezolizumab to platinum-based chemotherapy for first-line treatment of non-squamous non-small-cell lung cancer significantly improves overall survival compared with platinum-based chemotherapy alone. Results from a recent phase 3 trial have demonstrated the clinical benefit of adding a PD-1 inhibitor to pemetrexed and platinum-based therapy in first-line non-squamous non-small-cell lung cancer.

We aimed to assess the efficacy and safety of atezolizumab plus chemotherapy (carboplatin plus nab-paclitaxel) versus chemotherapy alone as first-line therapy for patients with stage IV non-squamous non-small-cell lung cancer who have not previously received chemotherapy.

Methods

Study design and participants

IMpower130 was a multicentre, randomised, open-label, phase 3 study done in 131 academic medical centres and community oncology practices in North America (Canada and the USA), western Europe (Belgium, France, Germany, Italy, and Spain), and Israel (appendix pp 25–28).

Patients were aged 18 years or older, and had histologically or cytologically confirmed stage IV non-squamous non-small-cell lung cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and received no previous chemotherapy for stage IV non-squamous non-small-cell lung cancer. Patients with a sensitising mutation in the *EGFR* gene or *ALK* fusion oncogene must have had disease progression (during or after treatment) based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or intolerance to treatment with at least one tyrosine kinase inhibitor (discontinued >7 days before randomisation). Patients with unknown *EGFR* or *ALK* status were required to have had locally or centrally assessed testing at screening. Patients were required to have known PD-L1 tumour status, determined by centrally assessed immunohistochemistry either on archival tumour tissue or tissue obtained at screening. Patients with treated asymptomatic CNS metastases were also eligible, but those with active or untreated CNS metastases, spinal cord compression, or leptomeningeal disease were ineligible. Eligible patients were required to have adequate haematological and end-organ function, which was defined as an absolute neutrophil count of 1500 cells per μL or more without granulocyte colony-stimulating factor support; a lymphocyte count of 500 cells per μL or more; a platelet count of 100 000 per μL or more without transfusion; haemoglobin concentration of 9·0 g/dL or more (patients could be transfused to meet this criterion); international normalised ratio or activated partial thromboplastin time of 1·5 × upper limit of normal (ULN) or less (only applied to patients who were not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should have been on a stable dose); aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase 2·5 × ULN or less (with the following exceptions: aspartate aminotransferase or alanine aminotransferase ≤5 × ULN in patients with documented liver metastases; alkaline phosphatase ≤5 × ULN in patients with documented liver or bone metastases); serum bilirubin 1·25 × ULN or less (patients with known Gilbert disease who had serum bilirubin level ≤3 × ULN could be enrolled); and serum creatinine 1·5 × ULN or less. Previous neoadjuvant or adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease were permitted if patients had a treatment-free interval of 6 months or more from randomisation.

Patients were ineligible if they had autoimmune disease. Patients with malignancies other than non-small-cell lung cancer within the 5 years before randomisation were excluded, as were patients with a history of interstitial lung disease (including idiopathic pulmonary fibrosis, organising pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis at screening). Previous treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 therapeutic antibodies, and anti-PD-L1 therapeutic antibodies was not permitted (see appendix pp 135–42 for the complete list of inclusion and exclusion criteria). See the appendix for the study protocol.

See Online for appendix

IMpower130 was done in accordance with the International Conference on Harmonisation (ICH) E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, and the ICH E2A guideline for expedited clinical safety data reporting. Each site was required to submit written documentation of protocol approval by the local ethics committee or institutional review board before initiating the study. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned with permuted block randomisation (block size of six) and an interactive voice or web response system (IxRS; Bracket; San Francisco, CA, USA). Patients were randomly assigned (2:1) to receive atezolizumab plus chemotherapy or chemotherapy alone, and stratification factors were sex (male *vs* female), presence of liver metastases at baseline (yes *vs* no), and PD-L1 tumour expression by immunohistochemistry (tumour cells TC3 and any tumour-infiltrating immune cells [IC] *vs* TC0/1/2 and IC2/3 *vs* TC0/1/2 and IC0/1).

Procedures

Patients received induction atezolizumab treatment (1200 mg intravenously every 3 weeks) in combination with chemotherapy comprising carboplatin (area under the curve 6 mg/mL per min every 3 weeks) plus nab-paclitaxel (100 mg/m² intravenously every week) or chemotherapy alone according to the same schedule for four or six 21-day cycles. The number of induction treatment cycles (four or six) was at the discretion of the investigator and determined or documented before randomisation. Following induction, patients in the atezolizumab plus chemotherapy group received maintenance treatment with 1200 mg intravenous atezolizumab and patients in the chemotherapy group received best supportive care or pemetrexed switch

maintenance therapy, at the investigator's discretion. In the atezolizumab plus chemotherapy group, maintenance therapy was administered until investigator-assessed loss of clinical benefit or toxicity, and in the chemotherapy group pemetrexed maintenance was administered until disease progression, as per RECIST (version 1.1), or toxicity. Atezolizumab dose reductions were not allowed; patients could temporarily suspend study treatment with atezolizumab for up to 105 days beyond the last dose if they had an adverse event that required a dose to be withheld. If a patient was tapered off steroids used to treat adverse events, atezolizumab could be withheld beyond 105 days from the last dose until steroids were discontinued or reduced to prednisone dose (or dose equivalent) 10 mg or less per day. The acceptable length of interruption was dependent on agreement between the investigator and the study's medical monitor. Nab-paclitaxel and carboplatin doses could be reduced or withheld for specific toxicities according to the protocol (appendix).

Crossover to receive atezolizumab at disease progression was permitted only for patients in the chemotherapy group enrolled before June 15, 2016 (versions 1–4 of the protocol), providing that they continued to meet eligibility criteria. The option for patients in the chemotherapy group to receive atezolizumab under the auspices of the protocol after failure of first-line study treatment was removed to minimise confounding of the co-primary overall survival endpoint that was added to protocol in version 5 (June 15, 2016).

Permitted concomitant therapies included corticosteroid treatment (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency.

Patients underwent tumour assessments at baseline and a CT scan (contrast enhanced unless contraindicated) or MRI of the thorax and abdomen every 6 weeks (±7 days) for the first 48 weeks following cycle 1, day 1, regardless of dose delays; after 48 weeks, tumour assessment was required every 9 weeks (±7 days). Patients had tumour assessments until radiographic disease progression as per RECIST, version 1.1 (or loss of clinical benefit in patients receiving atezolizumab who continued atezolizumab after radiographic disease progression), withdrawal of consent, study termination by sponsor, or death; whichever occurred first. Patients who discontinued treatment for reasons other than radiographic disease progression continued scheduled tumour assessments until radiographic disease progression (or loss of clinical benefit for patients receiving atezolizumab who had continued atezolizumab after radiographic disease progression), withdrawal of consent, study termination by sponsor, or death; whichever occurred first, regardless of whether patients had started a new anticancer therapy. Patients in all treatment groups had a mandatory tumour biopsy sample collection, unless not clinically feasible, at the first evidence of radiographic disease progression. An independent review facility did a blinded radiology review of the imaging data, and tumour response and progression were independently assessed as a sensitivity analysis.

Haematology and serum chemistry tests were done at screening, during the induction phase, during the maintenance phase, and at the treatment discontinuation visit. Coagulation tests were done at screening and at the treatment discontinuation visit.

All adverse events were assessed at baseline, during the induction period, during the maintenance phase, at the treatment discontinuation visit, and during survival follow-up. Incidence, nature, and severity of adverse events were graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

PD-L1 expression was centrally assessed by immunohistochemistry with the VENTANA PD-L1 (SP142) Assay (Ventana Medical Systems, Tucson, AZ, USA), which is optimised to detect PD-L1 on tumour cells and tumour-infiltrating immune cells.[7] PD-L1 expression was assessed by scoring the percentage of PD-L1-expressing tumour cells (TC0: <1% of tumour cells expressing PD-L1; TC1: ≥1% and <5% of tumour cells expressing PD-L1; TC2: ≥5% and <50% of tumour cells expressing PD-L1; TC3: ≥50% of tumour cells expressing PD-L1) and on tumour-infiltrating immune cells, by scoring immune cells expressing PD-L1 as a percentage of tumour area (IC0: <1% of immune cells expressing PD-L1; IC1: ≥1% and <5% of immune cells expressing PD-L1; IC2: ≥5% and <10% of immune cells expressing PD-L1; IC3: ≥10% of immune cells expressing PD-L1). PD-L1 assays were stored and processed centrally by Targos Molecular Pathology GmBH (Kassel, Germany).

Outcomes

The reported co-primary endpoints were investigator-assessed progression-free survival and overall survival in randomised patients with *EGFR*^{wt} or *ALK*^{wt} tumours (ie, the wild-type population).

Secondary efficacy endpoints included investigator-assessed progression-free survival and overall survival in the intention-to-treat population; investigator-assessed progression-free survival and overall survival according to PD-L1 expression in the intention-to-treat wild-type and intention-to-treat populations; objective response and duration of response in the intention-to-treat wild-type population; 1-year and 2-year overall survival (to be reported separately at a later date); time to deterioration in patient-reported lung cancer symptoms, as determined by European Organisation for Research and Treatment of Cancer scales; and change from baseline in patient-reported lung cancer symptoms as determined by Symptoms in Lung Cancer scales (to be reported separately at a later date).

A complete list of secondary and exploratory endpoints is included in the appendix (pp 2, 202–04).

Statistical analysis

The sample size was based on the number of events required to demonstrate efficacy for both progression-free survival and overall survival (co-primary endpoints). We aimed to randomise about 715 patients, and about 650 patients were expected to be in the intention-to-treat wild-type population.

To control the overall type I error rate for the two-sided test at 0·05, we allocated a two-sided α of 0·006 to progression-free survival and a two-sided α of 0·044 to overall survival. We tested the primary comparison of progression-free survival at a two-sided α level of 0·006 in the intention-to-treat wild-type population. We tested the primary comparison of overall survival in the intention-to-treat wild-type population at the allocated α, together with the α recycled from the progression-free survival analysis if the progression-free survival comparison was significant (appendix p 3).[14]

One interim analysis was planned for the co-primary endpoint of overall survival. The final progression-free survival analysis and the interim overall survival analysis were planned when about 352 overall survival events were observed in intention-to-treat wild-type population. We calculated the stopping boundaries for overall survival analyses using the LanDeMets approximation to the Pocock boundary (the actual stopping boundary for the interim overall survival analysis was calculated to be 0·0425). If overall survival in the intention-to-treat wild-type population was significant, progression-free survival and overall survival were to be formally tested in the intention-to-treat population following the same α-spending algorithm and allocation ratio (3:22) in the intention-to-treat wild-type population. An overview of the analysis populations is detailed in the appendix (p 2). We compared progression-free survival and overall survival between treatment groups using a stratified log-rank test; we estimated the hazard ratio (HR) and 95% CI for progression-free survival and overall survival for treatment comparisons using a stratified Cox regression model. We used Kaplan-Meier methodology to estimate the median progression-free survival and median overall survival for each treatment group. We used Brookmeyer-Crowley methodology to estimate the 95% CI for the median progression-free survival and the median overall survival for each treatment group.[15]

We calculated an estimate of overall response and its 95% CI using the Clopper-Pearson method for each treatment group. We determined CIs for the difference in overall response between the two groups using the normal approximation to the binomial distribution. We compared the overall response between the two groups using the stratified Cochran-Mantel-Haenszel test. We estimated the duration of response using Kaplan-Meier methodology.

The safety population included all treated patients, defined as randomised patients who had received any protocol treatment. Patients were grouped according to whether any full or partial dose of atezolizumab was received, including when atezolizumab was received in error.

An independent data monitoring committee evaluated and reviewed unblinded safety data on a periodic basis, approximately every 6 months from the first patient enrolled. The sponsor was blinded to the efficacy results until the final analysis of progression-free survival.

We analysed data using SAS (version 9.4), R (version 3.3.1), and Spotfire (version 7.7).

This trial is registered with ClinicalTrials.gov, number NCT02367781.

Role of the funding source

The study sponsor was involved in the study design, protocol development, regulatory and ethics approvals, safety monitoring and reporting, and data collection, analysis, and interpretation. The employees of the sponsor collected, managed, and analysed data, had access to the raw data, and were involved in the writing of the report. All authors had full access to all study data and interpreted and analysed the data. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 16, 2015, and Feb 13, 2017, 1247 patients were assessed for eligibility, with 523 ineligible for enrolment (figure 1).

724 patients were randomly assigned and 723 were included in the intention-to-treat population (one patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population). The intention-to-treat population comprised 483 patients in the atezolizumab plus chemotherapy group and 240 patients in the chemotherapy group. The intention-to-treat wild-type population comprised 451 patients in the atezolizumab plus chemotherapy group and 228 patients in the chemotherapy group. The safety population included 473 patients in the atezolizumab plus chemotherapy group and 232 patients in the chemotherapy group.

Baseline characteristics were generally balanced between treatment groups, including in the PD-L1 diagnostic subgroups (table 1). Of note, use of corticosteroids (including all use, irrespective of reason) was similar in both groups (359 [80%] of 451 patients in the atezolizumab plus chemotherapy group and 181 [79%] of 228 in the chemotherapy group).

In the intention-to-treat wild-type population, the median follow-up was similar between groups (18·5 months [IQR 15·2–23·6] in the atezolizumab plus chemotherapy group and 19·2 months [15·4–23·0] in the chemotherapy group). At data cutoff (on March 15, 2018), 347 (77%) of 451 patients in the atezolizumab plus chemotherapy group and 198 (87%) of 228 patients in the chemotherapy group had a progression-free survival

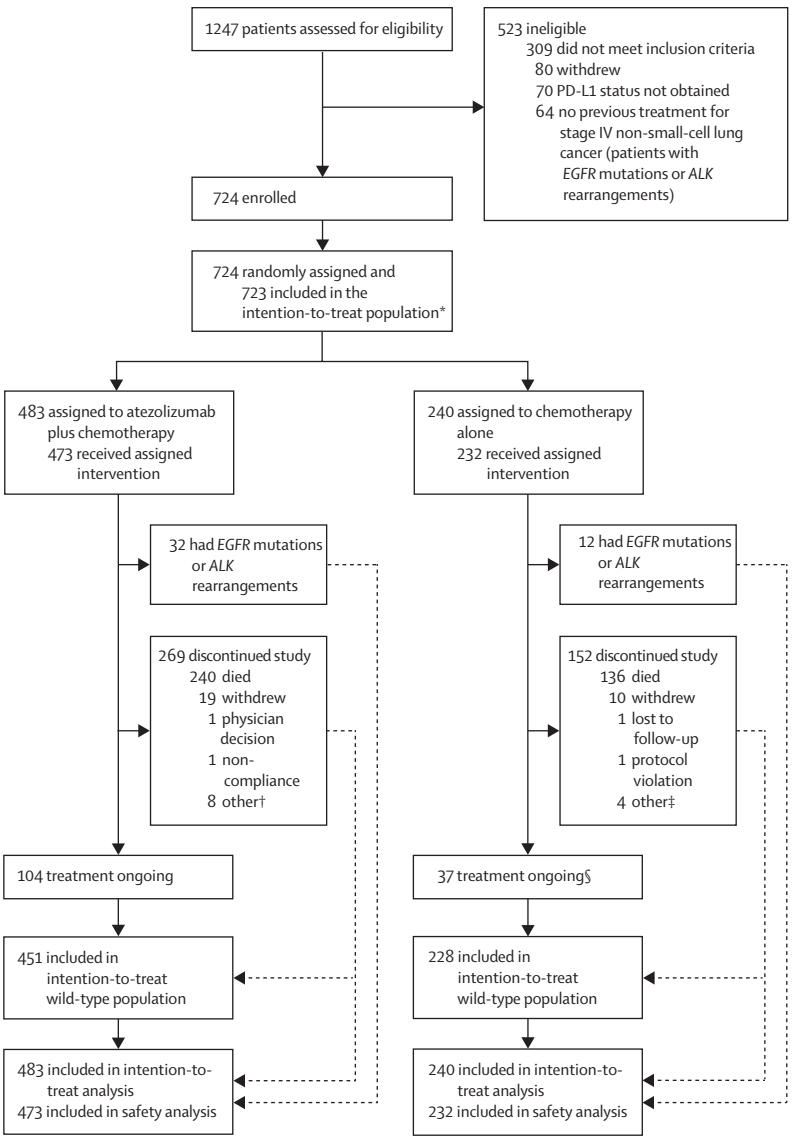

Figure 1: **Trial profile**

*One patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population. †Eight patients were discontinued from the study: five patients were randomly assigned in error (no study drugs administered), one patient moved to another facility, one patient died before drug administration, and one patient had a long hospital stay before the first dose of study drug. ‡Four patients were randomly assigned in error and were discontinued from the study (no study drug administered). §Includes patients who crossed over to receive atezolizumab.

event. Median investigator-assessed progression-free survival was 7·0 months (95% CI 6·2–7·3) in the atezolizumab plus chemotherapy group and 5·5 months (4·4–5·9) in the chemotherapy group (stratified HR 0·64 [95% CI 0·54–0·77]; p<0·0001]; figure 2A). 226 (50%) of 451 patients in the atezolizumab plus chemotherapy group and 131 (57%) of 228 patients in the chemotherapy group had died. Median overall survival was 18·6 months (95% CI 16·0–21·2) in the atezolizumab plus chemotherapy group and 13·9 months (12·0–18·7) in the chemotherapy group (stratified HR 0·79 [95% CI 0·64–0·98]; p=0·033; figure 2B). Analyses of progression-free survival assessed by an independent review facility were similar to the primary analysis (appendix p 4).

In the intention-to-treat wild-type population, 176 (39%) of 451 patients in the atezolizumab plus chemotherapy group and 151 (66%) of 228 patients in the chemotherapy group received cancer therapy of any category after disease progression (appendix p 5). In the chemotherapy group, 135 (59%) of 228 patients received immunotherapy after disease progression, including atezolizumab at crossover as per the protocol (93 [41%] of 228 patients in the chemotherapy group). In the atezolizumab plus chemotherapy group, 33 (7%) of 451 patients received further treatment with immunotherapy agents.

As the primary analysis of overall survival crossed the prespecified boundary, progression-free survival and overall survival could be formally tested in the intention-to-treat population, according the same α-spending allocation and algorithm per the co-primary analyses. In the intention-to-treat population, median follow-up was similar between groups (18·5 months [IQR 15·2–23·6] in the atezolizumab plus chemotherapy group and 18·8 months [15·3–23·3] in the chemotherapy group). Median investigator-assessed progression-free survival and median overall survival are shown in figure 3.

Subgroup analyses showed consistent overall survival (figure 4) and progression-free survival (figure 5) benefit with atezolizumab across the majority of clinical subgroups, except for patients with liver metastases, in whom atezolizumab plus chemotherapy did not show improved overall survival versus chemotherapy alone, and for patients with *EGFR* or *ALK* genomic alterations (appendix p 6). With respect to the PD-L1 subgroups, treatment benefit was observed in terms of overall survival and progression-free survival in the intention-to-treat and intention-to-treat wild-type populations, regardless of PD-L1 expression (appendix p 7).

In the intention-to-treat wild-type population, the proportion of patients (who had measurable disease at baseline) with a confirmed objective response was higher in the atezolizumab plus chemotherapy group (220 [49·2%, 95% CI 44·5–54·0] of 447 patients) than in the chemotherapy group (72 [31·9%, 25·8–38·4] of 226 patients; odds ratio 2·07 [95% CI 1·48–2·89]; appendix p 8). More patients in the atezolizumab plus chemotherapy group compared with the chemotherapy group had a complete response (11 [2%] of 447 *vs* three [1%] of 226) or a partial response (209 [47%] of 447 *vs* 69 [31%] of 226; appendix p 8). More patients in the chemotherapy group, compared with the atezolizumab plus chemotherapy group, had stable disease (86 [38] of 226 *vs* 136 [30%] of 447) or progressive disease (41 [18%] of 226 *vs* 49 [11%] of 447; appendix p 8). Treatment with atezolizumab plus chemotherapy resulted in improved confirmed duration of response compared with chemotherapy alone (appendix pp 8–9). Among responders, the

	Intention-to-treat population		Intention-to-treat wild-type population	
	Atezolizumab plus chemotherapy group (n=483)	Chemotherapy group (n=240)	Atezolizumab plus chemotherapy group (n=451)	Chemotherapy group (n=228)
Age, years	64 (18–86)	65 (38–85)	64 (18–86)	65 (38–85)
<65	245 (51%)	117 (49%)	227 (50%)	114 (50%)
65–74	186 (39%)	90 (38%)	174 (39%)	84 (37%)
75–84	50 (10%)	32 (13%)	48 (11%)	29 (13%)
≥85	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Sex				
Female	206 (43%)	102 (43%)	185 (41%)	94 (41%)
Male	277 (57%)	138 (58%)	266 (59%)	134 (59%)
Liver metastases at enrolment				
Present	74 (15%)	33 (14%)	69 (15%)	31 (14%)
Not present	409 (85%)	207 (86%)	382 (85%)	197 (86%)
Bone metastases	134 (28%)	68 (28%)	126 (28%)	63 (28%)
Race				
White	428 (89%)	222 (93%)	402 (89%)	210 (92%)
Black or African American	18 (4%)	8 (3%)	17 (4%)	8 (4%)
Asian	14 (3%)	3 (1%)	12 (3%)	3 (1%)
Multiple	2 (<1%)	0	1 (<1%)	0
Unknown	21 (4%)	7 (3%)	19 (4%)	7 (3%)
Eastern Cooperative Oncology Group performance status				
0	204 (42%)	93 (39%)	189 (42%)	91 (40%)
1	278 (58%)	146 (61%)	261 (58%)	136 (60%)
2	0	1 (<1%)	0	1 (<1%)
Tobacco use history				
Never	64 (13%)	20 (8%)	48 (11%)	17 (7%)
Current	96 (20%)	53 (22%)	92 (20%)	51 (22%)
Previous	323 (67%)	167 (70%)	311 (69%)	160 (70%)
Pathology or histology				
Adenocarcinoma	462 (96%)	230 (96%)	432 (96%)	218 (96%)
Adenocarcinoma with neuroendocrine features	5 (1%)	4 (2%)	4 (1%)	4 (2%)
Adenosquamous	4 (1%)	0	4 (1%)	0
Bronchioloalveolar carcinoma	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Large cell	6 (1%)	2 (1%)	6 (1%)	2 (1%)
Sarcomatoid	2 (<1%)	0	2 (<1%)	0
Undifferentiated	1 (<1%)	2 (1%)	1 (<1%)	2 (1%)
Not applicable	1 (<1%)	0	1 (<1%)	0
Unknown	1 (<1%)	1 (<1%)	0	1 (<1%)
Planned cycles				
Four cycles	244 (51%)	127 (53%)	227 (50%)	119 (52%)
Six cycles	239 (49%)	113 (47%)	224 (50%)	109 (48%)
Patients with *EGFR* or *ALK* genomic aberrations	32 (7%)	12 (5%)	0	0
PD-L1 tumour expression				
PD-L1-high*	91 (19%)	43 (18%)	88 (20%)	42 (18%)
PD-L1-low†	139 (29%)	68 (28%)	128 (28%)	65 (29%)
PD-L1-negative‡	253 (52%)	129 (54%)	235 (52%)	121 (53%)

Data are median (range) or n (%). *TC3 or IC3: patients with PD-L1 expression in ≥50% of tumour cells or ≥10% of tumour-infiltrating immune cells. †TC1/2 or IC1/2: patients with PD-L1 expression in ≥1% and <50% of tumour cells or ≥1% and <10% of tumour-infiltrating immune cells. ‡TC0 and IC0: patients with PD-L1 expression in <1% of tumour cells and <1% of tumour-infiltrating immune cells.

Table 1: **Baseline characteristics**

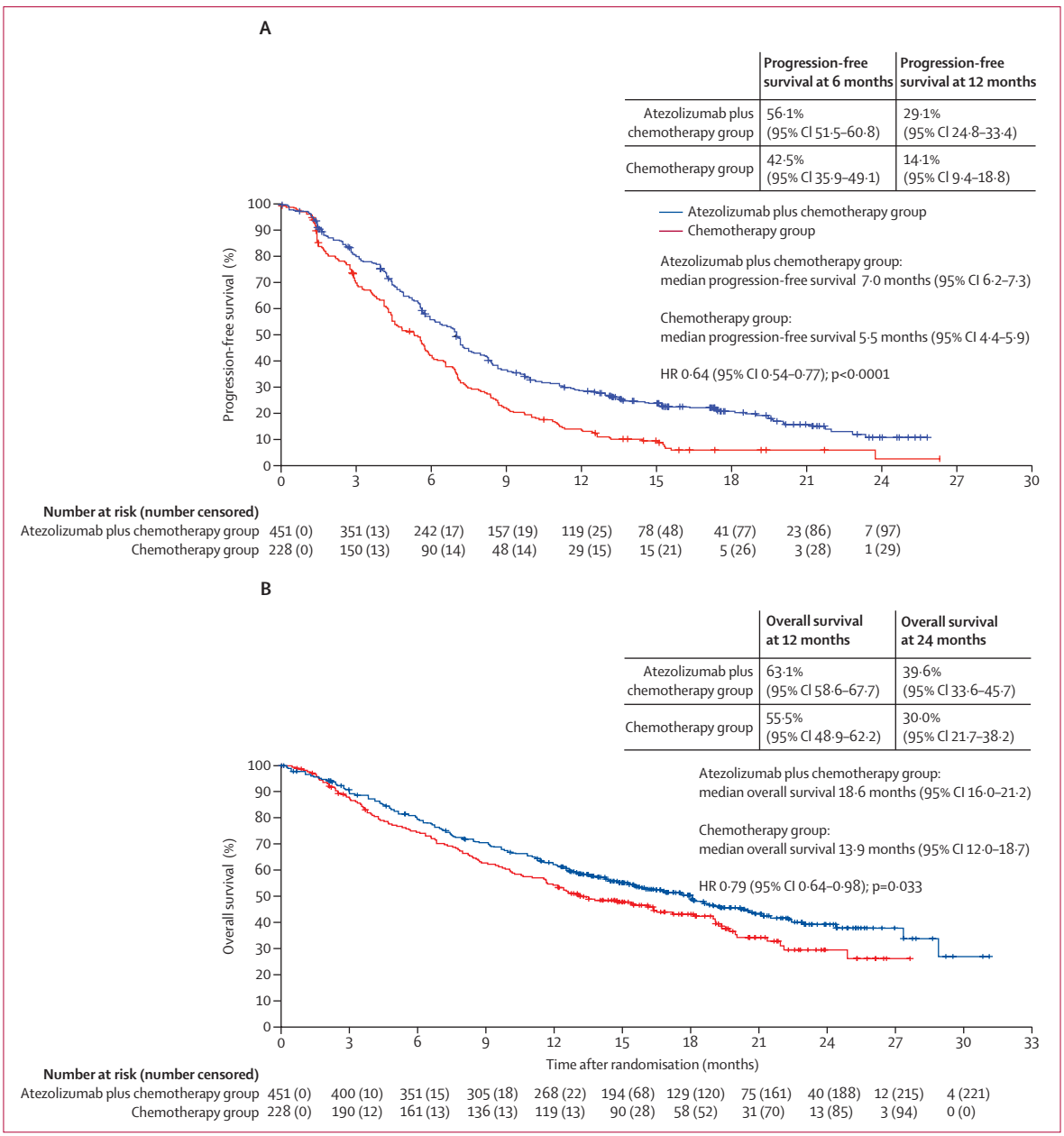

Figure 2: **Kaplan-Meier plots for progression-free survival (A) and overall survival (B) in the intention-to-treat wild-type population**
HR=hazard ratio.

median confirmed duration of response was longer in the atezolizumab plus chemotherapy group (8·4 months [95% CI 6·9–11·8]; n=220) than in the chemotherapy group (6·1 months [5·5–7·9]; n=72; appendix pp 8–9).

At the time of the analysis, 473 patients in the atezolizumab plus chemotherapy group and 232 patients in the chemotherapy group received at least one cycle of treatment (appendix p 10). Mean treatment duration in the atezolizumab plus chemotherapy group was 8·9 months (SD 7·2) for atezolizumab, 2·8 months (1·3) for nab-paclitaxel, and 2·4 months (1·2) for carboplatin. In the chemotherapy group, mean treatment duration was 2·6 months (SD 1·3) for nab-paclitaxel, 2·2 months (1·2) for carboplatin, and 4·9 months (4·1) for pemetrexed. Mean number of doses in the atezolizumab plus chemotherapy group was 12·8 (SD 9·8) for atezolizumab, 10·6 (4·4) for nab-paclitaxel, and 4·0 (1·4) for carboplatin. In the chemotherapy group, the mean number of doses was 10·0 (SD 4·4) for nab-paclitaxel, 3·7 (1·5) for carboplatin, and 7·7 (5·6) for pemetrexed. Mean dose intensities in the atezolizumab plus chemotherapy group were 92·4% (SD 8·2) for

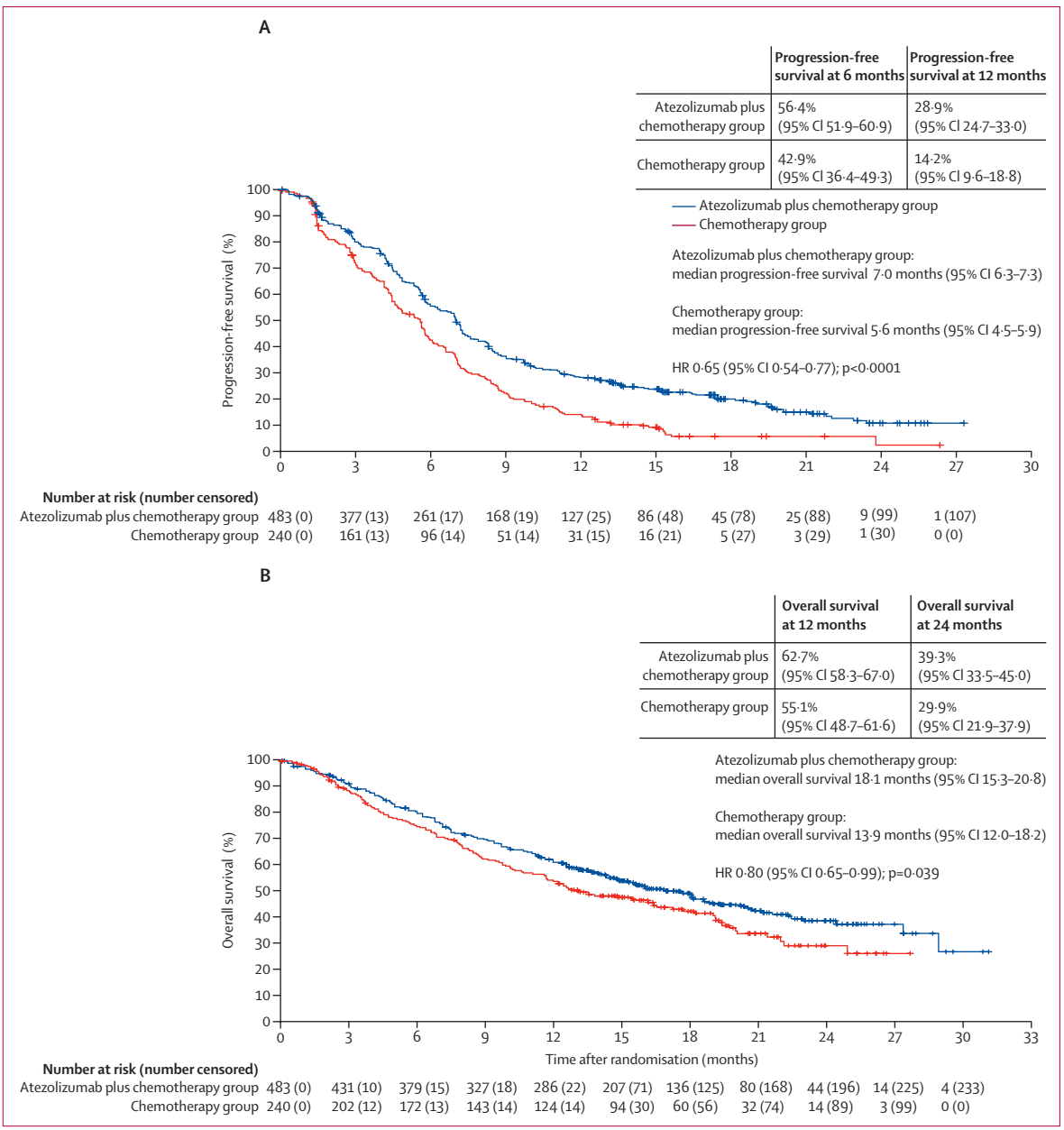

Figure 3: **Kaplan-Meier plots for progression-free survival (A) and overall survival (B) in the intention-to-treat population**
HR=hazard ratio.

atezolizumab, 82·6% (13·5) for nab-paclitaxel, and 90·2% (10·2) for carboplatin (appendix p 10). In the chemotherapy group, mean dose intensities were 84·2% (SD 13·8) for nab-paclitaxel, 91·3% (9·4) for carboplatin, and 96·7% (5·6) for pemetrexed (appendix p 10). The exposure to carboplatin and nab-paclitaxel was therefore similar in both treatment groups.

Safety data for the chemotherapy group included in this Article do not include data from the crossover phase, and adverse events reported as being treatment related were related to any component of treatment throughout this study. All-grade adverse events were reported in 471 (99·6%) of 473 patients in the atezolizumab plus chemotherapy group and 230 (99·1%) of 232 patients in the chemotherapy group (appendix pp 11–19), and grade 3–4 adverse events were reported in 381 (81%) of 473 patients in the atezolizumab plus chemotherapy group and 164 (71%) of 232 patients in the chemotherapy group (appendix pp 11–18). Adverse events related to any treatment (as determined by the investigator) occurred in 455 (96%) of 473 patients in the atezolizumab plus chemotherapy group and 215 (93%)

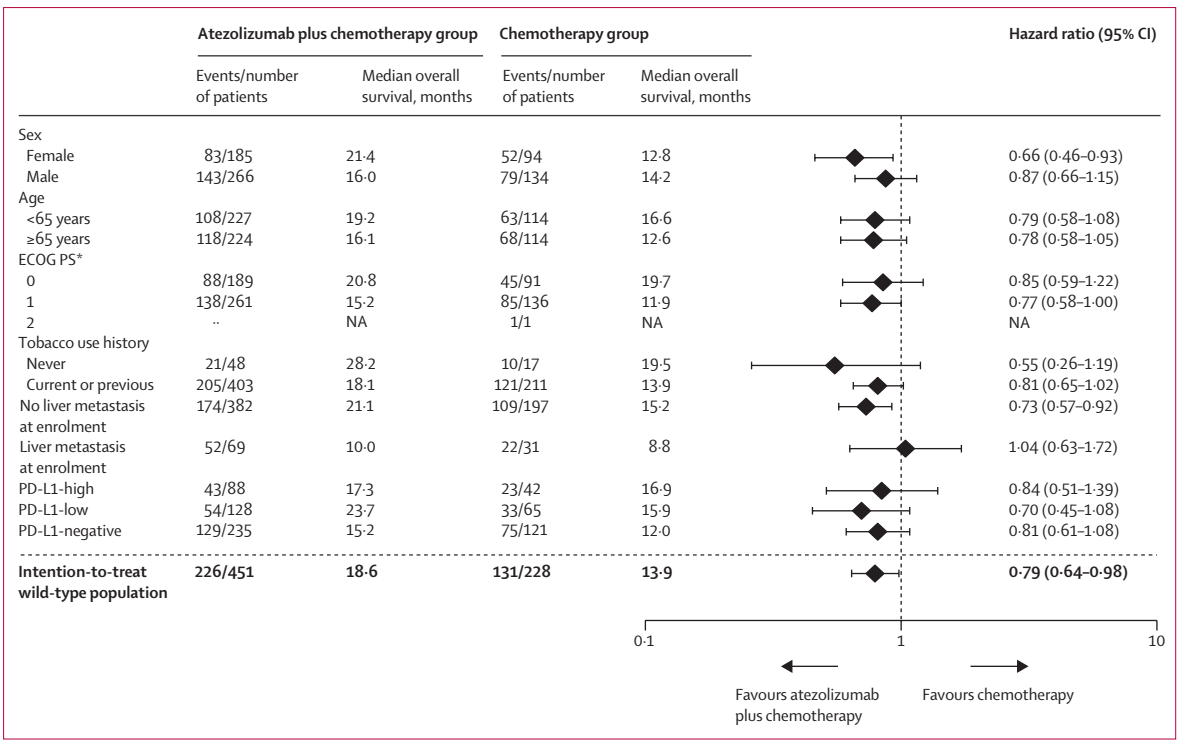

Figure 4: **Forest plot of hazard ratios for overall survival in the intention-to-treat wild-type population according to patient characteristics at baseline**
Stratified hazard ratio (95% CI) for overall intention-to-treat wild-type population; unstratified hazard ratios (95% CIs) for all other subgroups. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio. NA=not assessed. *One patient had an unknown ECOG PS.

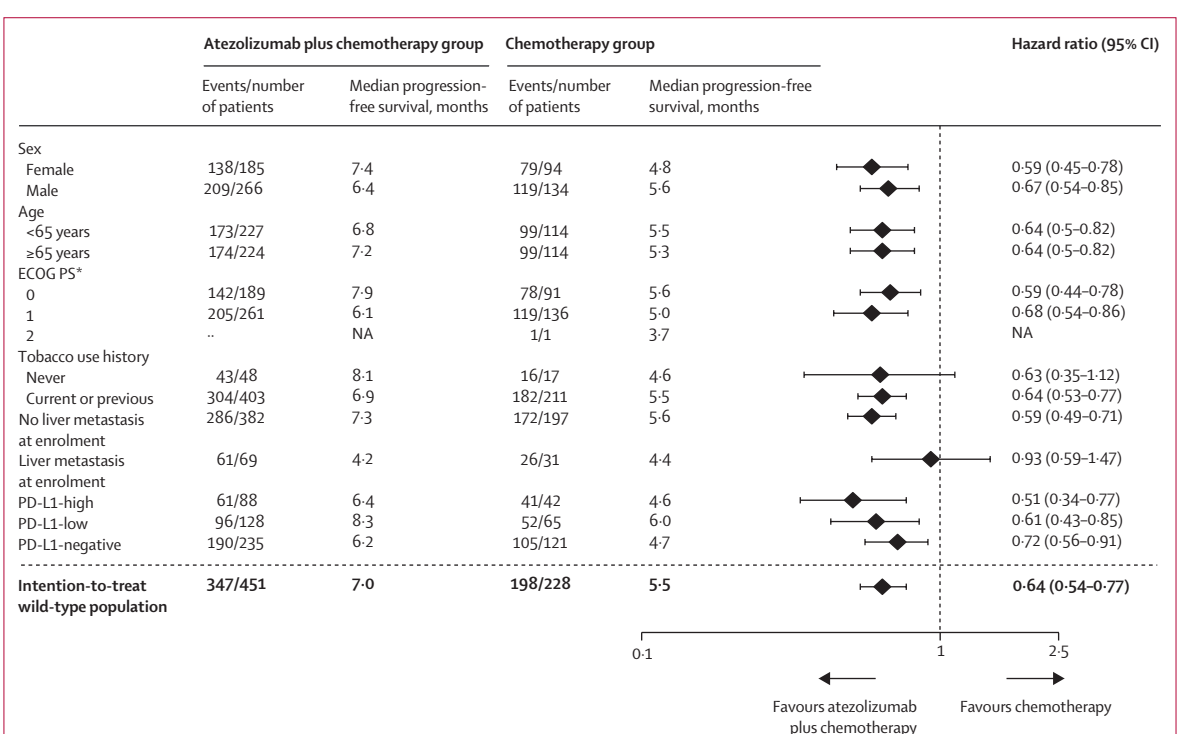

Figure 5: **Forest plot of hazard ratios for progression-free survival in the intention-to-treat wild-type population according to patient characteristics at baseline**
Stratified hazard ratio (95% CI) for the overall intention-to-treat wild-type population; unstratified hazard ratios (95% CIs) for all other subgroups. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio. NA=not assessed. *One patient had an unknown ECOG PS.

	Atezolizumab plus chemotherapy group (n=473)				Chemotherapy group (n=232)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Treatment-related adverse events	101 (21%)	237 (50%)	109 (23%)	8 (2%)	74 (32%)	109 (47%)	31 (13%)	1 (<1%)
Neutropenia*	66 (14%)	92 (19%)	60 (13%)	0	39 (17%)	47 (20%)	18 (8%)	0
Anaemia	110 (23%)	138 (29%)	0	0	62 (27%)	46 (20%)	1 (<1%)	0
Neutrophil count decreased*	36 (8%)	37 (8%)	20 (4%)	0	14 (6%)	11 (5%)	8 (3%)	0
Thrombocytopenia†	82 (17%)	30 (6%)	15 (3%)	0	43 (19%)	12 (5%)	3 (1%)	0
Platelet count decreased†	68 (14%)	31 (7%)	6 (1%)	0	24 (10%)	10 (4%)	4 (2%)	0
Fatigue	156 (33%)	28 (6%)	1 (<1%)	0	77 (33%)	14 (6%)	0	0
White blood cell count decreased	20 (4%)	25 (5%)	6 (1%)	0	10 (4%)	6 (3%)	1 (<1%)	0
Diarrhoea	127 (27%)	22 (5%)	1 (<1%)	0	44 (19%)	11 (5%)	0	0
Nausea	194 (41%)	13 (3%)	0	0	92 (40%)	4 (2%)	0	0
Vomiting	90 (19%)	9 (2%)	0	0	30 (13%)	3 (1%)	0	0
Asthenia	52 (11%)	9 (2%)	0	0	28 (12%)	3 (1%)	0	0
Decreased appetite	100 (21%)	7 (1%)	0	0	42 (18%)	4 (2%)	0	0
Hypomagnesaemia	57 (12%)	4 (1%)	1 (<1%)	0	21 (9%)	3 (1%)	0	0
Constipation	72 (15%)	1 (<1%)	0	0	33 (14%)	0	0	0
Alopecia	145 (31%)	0	0	0	61 (26%)	0	0	0
Dysgeusia	51 (11%)	0	0	0	11 (5%)	0	0	0

Data are n (%). Safety data are included for the chemotherapy group for patients up until crossover. Adverse events with an incidence of ≥10% in any group or grade 3–4 severity with incidence of ≥5% in any group are shown. All grade 3–5 events are listed in appendix pp 12–18. The causes of treatment-related deaths in the atezolizumab plus chemotherapy group were reported as pneumonitis (n=2), death (n=1), septic shock (n=1), myocardial infarction (n=1), cardiac arrest (n=1), ventricular tachycardia (n=1), and hepatic cirrhosis (n=1). The cause of the treatment-related death in the chemotherapy group was sepsis (n=1). *Neutrophil count decreased and neutropenia represent the same medical concept but were reported using different terminology by the investigators. †Platelet count decreased and thrombocytopenia represent the same medical concept but were reported using different terminology by the investigators.

Table 2: **Treatment-related adverse events**

of 232 patients in the chemotherapy group (table 2; appendix p 11).

The most common grade 3 or worse treatment-related adverse events were neutropenia (152 [32%] of 473 in the atezolizumab plus chemotherapy group *vs* 65 [28%] of 232 in the chemotherapy group), anaemia (138 [29%] *vs* 47 [20%]), and decreased neutrophil count (57 [12%] *vs* 19 [8%]; table 2). Fatal adverse events (of any causality) were reported in 25 (5%) of 473 patients in the atezolizumab plus chemotherapy group and 13 (6%) of 232 patients in the chemotherapy group (appendix p 19). Of note, the proportion of patients with adverse events leading to death related to infection or sepsis was similar in both treatment groups (eight [2%] of 473 patients in the atezolizumab plus chemotherapy group and five [2%] of 232 patients in the chemotherapy group). Deaths related to any treatment component according to the investigator occurred in eight (2%) of 473 patients treated with atezolizumab plus chemotherapy and one (<1%) of 232 patients treated with chemotherapy (table 2; appendix p 11). Further details are provided in the appendix (p 2).

Serious adverse events were observed in 240 (51%) of 473 patients in the atezolizumab plus chemotherapy group versus 88 (38%) of 232 patients in the chemotherapy group (appendix p 11 and p 20). Serious adverse events that were reported with a difference of 2% or more between the atezolizumab plus chemotherapy and chemotherapy groups were lung infection (14 [3%] of 473 patients *vs* one [<1%] of 232 patients), neutropenia (14 [3%] *vs* two [1%]), and diarrhoea (14 [3%] *vs* two [1%]; appendix p 20). Treatment-related serious adverse events were reported in 112 (24%) of 473 patients in the atezolizumab plus chemotherapy group and 30 (13%) of 232 patients in the chemotherapy group (appendix p 11 and p 21).

The proportion of patients with adverse events leading to discontinuation of any study treatment was 125 (26%) of 473 in the atezolizumab plus chemotherapy group compared with 51 (22%) of 232 patients in the chemotherapy group (appendix p 11 and p 22). The most common adverse events leading to discontinuation were thrombocytopenia, neutropenia, and fatigue (appendix p 22). No adverse events leading to withdrawal of any study treatment were reported with a 2% or more difference between the atezolizumab plus chemotherapy group and the chemotherapy group.

The proportion of patients experiencing adverse events leading to dose modification or interruption of any study treatment was 402 (85%) of 473 patients in the atezolizumab plus chemotherapy group versus 186 (80%) of 232 patients in the chemotherapy group (appendix p 11 and p 23). Adverse events leading to dose modification or interruption that were reported with difference of 2% or more in the atezolizumab plus chemotherapy group versus chemotherapy group were neutropenia (182 [38%] of 473 patients *vs* 83 [36%] of 232 patients), anaemia (77 [16%] *vs* 31 [13%]), decreased platelet count (71 [15%] *vs* 26 [11%]), pyrexia (23 [5%] *vs* three [1%]), diarrhoea

(43 [9%] *vs* 13 [6%]), nausea (21 [4%] *vs* 4 [2%]), pneumonitis (13 [3%] *vs* one [<1%]), dehydration (12 [3%] *vs* one [<1%]), and asthenia (ten [2%] *vs* 11 [5%]; appendix p 23).

Immune-related adverse events were reported in 213 (45%) of 473 patients in the atezolizumab plus chemotherapy group and the majority were grade 1–2 in severity (appendix p 24). The most common immune-mediated adverse events reported were rash in 114 (24%) patients, hypothyroidism in 70 (15%) patients, and hepatitis (includes adverse events of autoimmune hepatitis, hepatic failure, cirrhosis, and hepatocellular injury as well as adverse events of liver-related abnormal investigations [laboratory]) in 46 (10%) patients (appendix p 24).

Discussion

This phase 3, randomised IMpower130 study met its co-primary endpoints of demonstrating a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival in patients treated with atezolizumab plus chemotherapy compared with chemotherapy alone as a first-line treatment in patients with stage IV non-squamous non-small-cell lung cancer. In the intention-to-treat wild-type population, progression-free survival at the 12-month landmark was twice as high with atezolizumab plus chemotherapy compared with chemotherapy alone. Additionally, since overall survival crossed the prespecified boundary for significance, the secondary endpoints of overall survival and progression-free survival in the intention-to-treat population were formally tested, and these endpoints were also significantly different between groups.

The magnitude of overall survival benefit in reduction of the risk of death and median improvement of 4·7 months is clinically meaningful as well as significant. This outcome is robust, as the findings for the chemotherapy group are in line with historical controls. The overall survival advantage was observed, despite crossover to at least one subsequent line of immunotherapy by almost 60% of patients in the chemotherapy group. Patients in the chemotherapy group were also permitted to receive maintenance therapy with pemetrexed, where appropriate, to reflect modern standards of care. The difference in magnitude of the median point estimates observed between overall survival and progression-free survival has been observed in other studies of checkpoint inhibitors in non-small-cell lung cancer, and overall survival might be a more sensitive endpoint for cancer immunotherapy in non-small-cell lung cancer than progression-free survival.[9,16–18] The open-label nature of the study might have affected the treating physician's timing of the assessment of disease progression in the chemotherapy group, because the earlier versions of the protocol allowed patients in the chemotherapy group who had disease progression to cross over to receive atezolizumab as a second-line treatment. Analysis of the blinded, independent review of progression-free survival was, however, consistent with progression-free survival according to the investigators' assessment, so knowledge of treatment assignment was unlikely to have confounded the progression-free survival endpoint.

Although IMpower130 was not powered to detect a significant difference within subgroups, overall survival and progression-free survival benefit was observed across PD-L1 diagnostic subgroups irrespective of the level of PD-L1 expression. In the case of progression-free survival, there was a stepwise treatment effect according to PD-L1 expression; however, the CIs were mostly overlapping, suggesting consistency with the intention-to-treat wild-type primary population. In contrast to progression-free survival, no one PD-L1 subgroup drove the overall survival benefit, as HRs were similar across all diagnostic subgroups, including the subgroup with PD-L1-low expression. We hypothesise that the similar HRs resulted from the high number of patients in the chemotherapy group who crossed over to receive anti-PD-1 or anti-PD-L1 therapy following progression (almost 60% of patients). Progression-free survival was analysed before patients received additional anticancer therapies in the second line (or beyond) setting, whereas overall survival was assessed at the point of death or censoring and, therefore, might have been confounded or affected by the additional anticancer therapy received by patients up to that point. Patients with higher PD-L1 expression would be expected to respond more avidly to second-line (or beyond) immunotherapy, which might explain the similar HRs across PD-L1 subgroups. These findings are consistent with those of other first-line anti-PD-1 or anti-PD-L1 chemotherapy combination studies in PD-L1-unselected patients—eg, KEYNOTE-189,[19] KEYNOTE-407,[20] and IMpower150.[21]

Overall survival and progression-free survival benefits were observed in the majority of demographic subgroups, with the exception of patients with liver metastases and those with *EGFR* or *ALK* genomic alterations who had similar outcomes in both treatment groups; patients with liver metastasis at enrolment did not show improved overall survival when treated with atezolizumab plus chemotherapy versus chemotherapy alone. Although patient numbers for both subgroups (*EGFR* or *ALK* genomic alterations or liver metastasis at enrolment) were small in IMpower130, outcomes in patients with *EGFR* or *ALK* genomic alterations were consistent with previous studies in patients with non-small-cell lung cancer and *EGFR*-positive disease treated with anti-PD-1 or anti-PD-L1 therapy.[9,22,23] The only PD-1 or PD-L1 plus chemotherapy combination that has demonstrated benefit in patients with *EGFR* or *ALK* genomic alterations was in IMpower150 (atezolizumab plus bevacizumab and carboplatin and paclitaxel *vs* bevacizumab plus carboplatin and paclitaxel in chemotherapy-naive patients with

metastatic non-squamous non-small-cell lung cancer);[1,24] addition of bevacizumab to atezolizumab might confer activity to PD-L1 inhibition in this patient population.[1,25] As such, atezolizumab plus bevacizumab plus carboplatin and paclitaxel was recently approved by the US Food and Drug Administration in this indication, and is included in the European Society for Medical Oncology and National Comprehensive Cancer Network clinical practice guidelines.[1,2] Outcomes were also improved for patients with liver metastases in IMpower150, unlike in IMpower130, in which again, the addition of bevacizumab to the atezolizumab plus chemotherapy combination might be important.[25]

With respect to safety, chemotherapy exposure was similar in both treatment groups, suggesting that any treatment advantage for the atezolizumab plus chemotherapy group was not driven by suboptimal chemotherapy exposure in the chemotherapy group and that the administration of atezolizumab did not compromise the delivery of chemotherapy in the atezolizumab plus chemotherapy group. The safety profile of atezolizumab plus chemotherapy was consistent with the known adverse events related to single-agent therapy, with myelosuppression-related events reported most frequently in both groups. No new safety signals were observed.

There was no imbalance between treatment groups with respect to the proportion of patients with fatal adverse events (5% in the atezolizumab plus chemotherapy group *vs* 6% in the chemotherapy group). More patients died due to any component of study treatment in the atezolizumab plus chemotherapy group (2%) compared with the chemotherapy group (<1%), but further clinical investigation of these cases identified that four of the eight patients in the atezolizumab plus chemotherapy group had pre-existing cardiovascular conditions, which confounded these results.

Nab-paclitaxel was paired with carboplatin to form the chemotherapy backbone treatment because the requirement for corticosteroid premedication was expected to be reduced. Corticosteroids were thought to attenuate the potentially beneficial effects of immunotherapy at the time that the protocol was written, making carboplatin plus nab-paclitaxel a rational partner for investigation in combination with atezolizumab in this setting. As previously stated, almost 80% of patients in each group received corticosteroids, including anti-emetic prophylaxis for the carboplatin component. The observed use of corticosteroids in IMpower130 was higher than expected, and it is not possible to determine the effect of corticosteroid use, if any, on the outcome of the study. However, the significant and clinically meaningful efficacy outcomes observed in this study suggest that the omission of corticosteroids is not required when the atezolizumab plus chemotherapy (specifically, carboplatin plus nab-paclitaxel) regimen is administered to patients in the first-line treatment of non-squamous non-small-cell lung cancer.

It should be noted that both the European (European Society for Medical Oncology) and American (National Comprehensive Cancer Network) guidelines include the combination of nab-paclitaxel and platinum as an option for first-line treatment of non-squamous non-small-cell lung cancer, based on category 1 evidence.[1,2] The IMpower130 study results add to the growing body of data in favour of the use of first-line anti-PDL-1 or anti-PD-1 therapy in non-small-cell lung cancer. Anti-PD-1 monotherapy is becoming established as a standard of care for patients with PD-L1-positive tumours. However, the majority of patients have PD-L1-negative or PD-L1-unknown disease, and for these patients, conventional cytotoxic chemotherapy is still required as a partner to immunotherapy.[19,24] Oncologists will tailor the choice of platinum and partner chemotherapy on the basis of patient disease characteristics, the known toxicity profile of the chemotherapy combination, and patient comorbidities, along with the emergent data for checkpoint inhibitors as first-line non-small-cell lung cancer treatment. The results from IMpower130 suggest that atezolizumab plus chemotherapy is an additional first-line treatment option to be considered when formulating treatment plans for patients with advanced non-squamous non-small-cell lung cancer.

In summary, IMpower130 shows that the addition of atezolizumab to carboplatin plus nab-paclitaxel demonstrated a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival, with an acceptable safety profile, in chemotherapy-naive patients with stage IV non-squamous non-small-cell lung cancer with *EGFR*^{wt} and *ALK*^{wt} tumours, providing another treatment option for patients.

Contributors

All authors have reviewed the data analyses, contributed to data interpretation, contributed to drafting the work and revising the paper for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. HW, MM, HC, H-GK, DD, SM, and LW provided substantial contributions to the conception and design of the study. MM, MH, AM, AR, HC, H-GK, DD, SM, NR, TOL, and LW collected, acquired, or generated data. AM and AZ enrolled patients or provided study materials.

Declaration of interests

HW received personal fees from AstraZeneca, Genentech/Roche, and Pfizer (during the conduct of the study) and personal fees from Boehringer Ingelheim (outside the submitted work). MH received fees for participation in speaker bureaus from Boehringer Ingelheim, Bristol-Myers Squibb (BMS), AMAG, Incyte, and Herron (during the conduct of the study). AM received personal fees (honoraria) from Roche, Boehringer Ingelheim, Merck Sharp & Dohme (MSD), BMS, Pfizer, and AstraZeneca (outside the submitted work). AR received grants from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Pfizer, and Roche (outside the submitted work). H-GK received personal fees from MSD, Roche, and BMS (outside the submitted work). DD received payment (directly to Sarah Cannon Research Institute) from Roche (during the conduct of the study) and payment (directly to Sarah Cannon Research Institute for research) from E. R. Squibb & Sons, AstraZeneca, Boehringer Ingelheim, Genentech, Eli Lilly and Company, Novartis Pharmaceuticals, Pfizer, and Celgene (outside the submitted

work). SM received payment directly to study site from Roche/Genentech (during the conduct of the study). TM received personal fees for a speaker bureau from Roche/Genentech (outside the submitted work). AZ received grants from BMS; personal fees from BMS, Lilly, MSD, Roche, Boehringer Ingelheim, and AstraZeneca; and non-financial support from BMS, Roche, Boehringer Ingelheim, and AstraZeneca (outside the submitted work). NR received personal fees for speaker and advisory activities, and travel support, from Roche, BMS, MSD, Boehringer Ingelheim, AstraZeneca, Takeda, and Novartis (outside the submitted work). AhS received personal fees for a speaker panel from Millennium Pharma (outside the submitted work). AlS, WL, LW, and MK are employees of Genentech (during the conduct of the study). AIS, WL, and MK hold stock in Roche (during the conduct of the study). TOL is an employee of F. Hoffmann-La Roche (during the conduct of the study). VA is an employee of Roche Products (during the conduct of the study). FC received fees for membership of an advisory board from Roche, AstraZeneca, BMS, Pfizer, and MSD (outside the submitted work). All other authors declare no competing interests.

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: www.clinicalstudydatarequest.com. Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. 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 https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Acknowledgments

This work was funded by F. Hoffmann-La Roche (Basel, Switzerland). Support for third-party writing assistance for this manuscript, furnished by Islay Steele of Health Interactions, was provided by F. Hoffmann-La Roche. We thank the patients, their families, the nurses, and the investigators who participated in this study. We thank Helen Jessop (Roche Products, UK) for her assistance with the safety aspects of this manuscript, and the F. Hoffmann-La Roche IMpower130 study team.

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