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<https://doi.org/10.1038/s41591-025-03658-y>

Atezolizumab plus bevacizumab and chemotherapy in metastatic nonsquamous NSCLC: the randomized double-blind phase 3 IMpower151 trial

Received: 22 July 2024

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Accepted: 18 March 2025

Published online: 16 May 2025

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After the global approval of atezolizumab plus bevacizumab and chemotherapy as first-line metastatic nonsquamous non-small-cell lung cancer (nsqNSCLC) treatment, the IMpower151 ([NCT04194203](#)) trial was conducted in China to address regional differences. Chemotherapy-naïve patients with metastatic nsqNSCLC ($N = 305$) were randomized 1:1 to receive either atezolizumab, bevacizumab, carboplatin and paclitaxel or pemetrexed (ABCpem/Pac; $n = 152$) or placebo plus bevacizumab, carboplatin and pemetrexed or paclitaxel (BCPem/Pac; $n = 153$). The primary endpoint was investigator-assessed progression-free survival (INV-PFS); secondary endpoints included subgroup analyses of INV-PFS, independent review facility-assessed PFS, overall survival, and investigator-assessed objective response rate and duration of response per RECIST v.1.1. Most patients (97%) received pemetrexed, and 53% had *EGFR*⁺ tumors. Median INV-PFS for ABCpem/Pac versus BCPem/Pac was 9.5 versus 7.1 months (stratified hazard ratio: 0.84; 95% confidence interval: 0.65, 1.09; $P = 0.184$). INV-PFS across subgroups and independent review facility-assessed PFS were consistent with INV-PFS in the intention-to-treat population. Median overall survival was 20.7 versus 18.7 months in the ABCpem/Pac versus BCPem/Pac arms, respectively (stratified hazard ratio: 0.93; 95% confidence interval: 0.67, 1.28). Confirmed objective response rate with ABCpem/Pac versus BCPem/Pac was 48% versus 50%, respectively; median duration of response was 11.3 versus 8.3 months. Adverse events of special interest for atezolizumab were observed in 68% (grades 3 and 4: 11%) and 71% (grades 3 and 4: 7%) of patients receiving ABCpem/Pac and BCPem/Pac, respectively. The most common adverse events of special interest for atezolizumab in the ABCpem/Pac and BCPem/Pac arms were hepatitis (driven by laboratory abnormalities; mostly low grade), hypothyroidism and rash. Overall, IMpower151 did not meet its primary endpoint (INV-PFS) in metastatic nsqNSCLC. ABCpem/Pac was generally well tolerated, with no new safety signals. Trial registration number: ClinicalTrials.gov, [NCT02366143](#)

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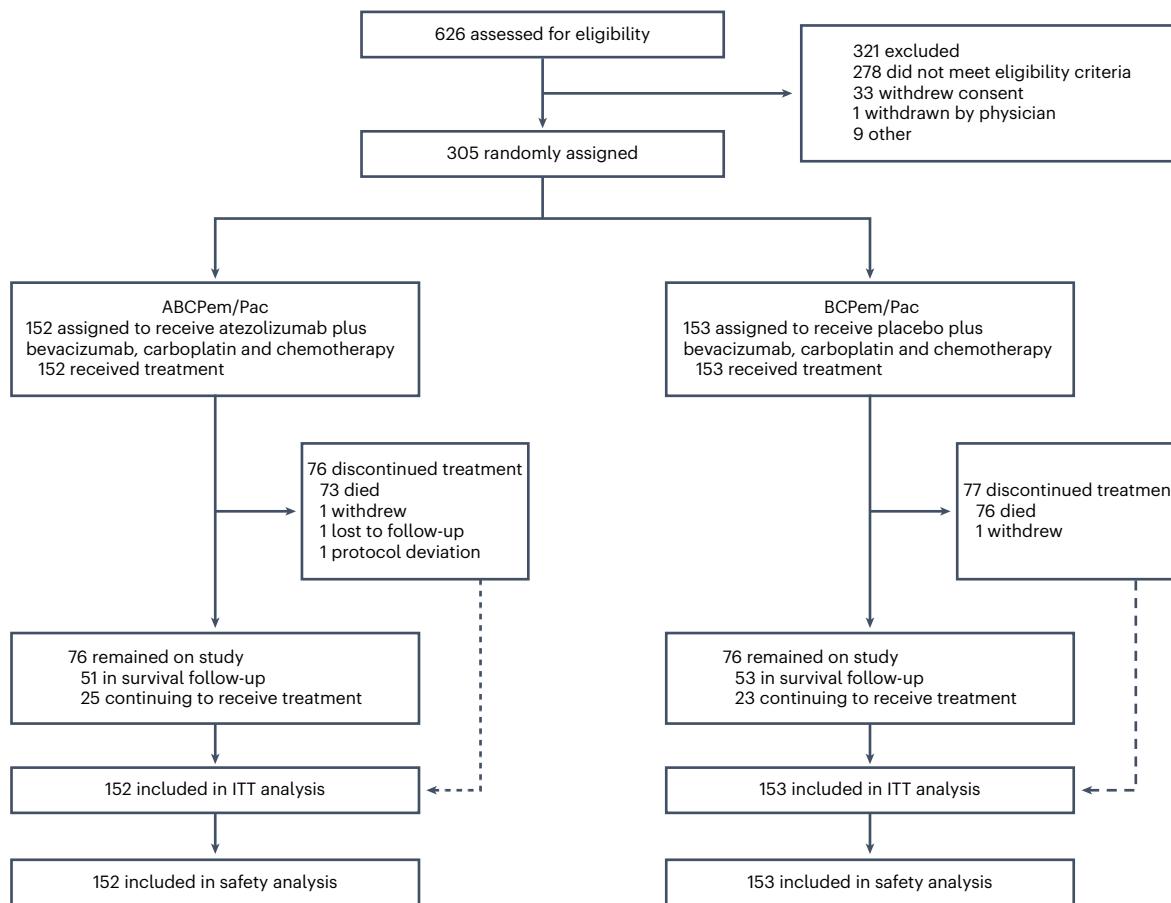


Fig. 1 | IMpower151 CONSORT diagram. Patient disposition. ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin and pemetrexed or paclitaxel; BCPem/Pac, placebo plus bevacizumab, carboplatin and pemetrexed or paclitaxel.

Lung cancer remains a leading cause of cancer mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for approximately 83% of all cases^{1,2}. In China in 2022, an estimated 1,060,600 patients were newly diagnosed with lung cancer and 733,300 patients with lung cancer died³.

The phase 3 IMpower150 study (NCT02366143) met both of its primary endpoints, demonstrating significant progression-free survival (PFS) and overall survival (OS) improvement with atezolizumab versus placebo combined with bevacizumab plus carboplatin and paclitaxel (ABCPac versus BCPac) in patients with metastatic nonsquamous (nsq) NSCLC without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic alterations⁴. PFS benefit was also observed in patients with *EGFR/ALK* genomic alterations (14% of patients), the majority of whom experienced failure on one line of prior tyrosine kinase inhibitor (TKI)^{4,5}. In the intention-to-treat (ITT) population, an improvement in OS favoring ABCPac over BCPac was observed across several baseline characteristics subgroups, with a greater OS benefit seen in male than in female patients⁵. Results from IMpower150 led to approval of this combination in the United States, the European Union and other regions as a first-line treatment for metastatic nsqNSCLC with or without *EGFR/ALK* genomic alterations^{6,7}.

Asian and Western patients with lung cancer have different characteristics for epidemiology (for example, risk factors, demographics and genetic susceptibility), clinical presentation, tumor biomarkers (for example, *EGFR* and Kirsten rat sarcoma virus mutation) and prognosis⁸. The exact mechanisms behind these differences are not clear⁸. In China, pemetrexed is used more commonly for the first-line treatment of nsqNSCLC than paclitaxel⁹.

To address regional differences in patients' genomic composition and clinical practice, the phase 3 IMpower151 study (NCT04194203) was conducted in China to evaluate the efficacy and safety of atezolizumab plus bevacizumab, carboplatin and pemetrexed or paclitaxel (ABCPem/Pac) versus placebo plus bevacizumab, carboplatin and pemetrexed or paclitaxel (BCPem/Pac) as a first-line treatment of metastatic nsqNSCLC regardless of sensitizing *EGFR/ALK* genomic alterations (henceforth referred to as *EGFR* mutations). In this article, we present the efficacy and safety results from the primary analysis of IMpower151, alongside observations from exploratory biomarker analyses.

Results

Patient disposition and baseline characteristics

From 9 April 2020 to 18 March 2022, a total of 305 patients (ITT population) out of 626 patients screened were enrolled in IMpower151 at 24 sites distributed across China and randomized to the ABCPem/Pac ($n = 152$) and BCPem/Pac ($n = 153$) arms (Fig. 1 and Supplementary Table 1). Baseline characteristics in the ITT population were generally well balanced between both arms (Table 1). The median age was 61 years (range: 30–76). Of the patients, 59% were male, 51% never smoked and 81% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1. Programmed death ligand-1 (PD-L1) expression status was tumor cell (TC) $\geq 1\%$ and TC $\geq 50\%$ in 52% and 30% of patients, respectively, and *EGFR* mutations were detected in 53% of patients. Approximately 97% of patients were selected by their investigator to receive pemetrexed. Of 162 patients, 81 (50%) received ≥ 2 prior lines of *EGFR* or *ALK* TKI treatment. Of 157 patients who received prior *EGFR* TKI treatment, 66% received a third-generation TKI.

Table 1 | Baseline characteristics in the ITT population

	ABCPEm/Pac (n=152)	BCPEm/Pac (n=153)
Median age (range), yr	61 (30–76)	61 (31–75)
Age <65 yr, n (%)	100 (65.8)	98 (64.1)
Sex, n (%)		
Female	62 (40.8)	62 (40.5)
Male	90 (59.2)	91 (59.5)
Tobacco use history, n (%)		
Never	82 (53.9)	75 (49.0)
Current	11 (7.2)	5 (3.3)
Previous	59 (38.8)	73 (47.7)
ECOG PS, n (%)		
0	27 (17.8)	31 (20.3)
1	125 (82.2)	122 (79.7)
Selected by investigator to receive pemtrexed, n (%)	149 (98.0)	148 (96.7)
PD-L1 expression by SP263 (central), n (%) ^a		
TC <1%	78 (51.3)	68 (44.4)
TC ≥1%	74 (48.7)	85 (55.6)
TC <50%	106 (69.7)	107 (69.9)
TC ≥50%	46 (30.3)	46 (30.1)
Liver metastasis, n (%)	17 (11.2)	17 (11.1)
Brain metastasis, n (%)	13 (8.6)	20 (13.1)
Bone metastasis, n (%)	74 (48.7)	78 (51.0)
EGFR WT, n (%) ^{a,b}	71 (46.7)	71 (46.4)
EGFR mutations, n (%) ^{c,d}	81 (53.3)	82 (53.6)
ALK rearrangement	2 (1.3)	3 (2.0)
EGFR mutation	79 (52.0)	79 (51.6)
T790M ^d	14 (17.7)	8 (10.1)
Exon 19 del ^e	50 (63.3)	46 (58.2)
L858R ^e	26 (32.9)	31 (39.2)
Other ^f	5 (6.3)	2 (2.5)
Prior lines of TKI treatment, n ^g	79 ^{h,i}	83 ⁱ
1, n (%)	37 (46.8)	44 (53.0)
≥2, n (%)	42 (53.2)	39 (47.0)
Prior EGFR TKI treatment, n	78 ^j	79
1G or 2G TKI only, n (%)	22 (28.2)	31 (39.2)
3G TKI only, n (%)	14 (17.9)	10 (12.7)
1G or 2G TKI, then 3G TKI, n (%)	42 (53.8)	38 (48.1)

1G, first generation; 2G, second generation; 3G, third generation. ^aRandomization was stratified by genotype of EGFR or ALK gene (genomic alterations versus WT) and PD-L1 expression (TC <50% versus TC ≥50% by the SP263 immunohistochemistry assay). ^bIncludes patients with ALK WT tumors. ^cIncludes patients with tumors harboring ALK rearrangements. ^dFor central testing, fresh biopsies taken after the last line of TKI treatment and before study enrollment were preferred. If unavailable, archival samples were acceptable. Therefore, the samples tested centrally for patients who received 3G TKI as a second-line or beyond treatment were not representative of the patient's tumor mutational landscape at the time of initiation of the 3G TKI treatment. ^eTwo patients in the ABCPEm/Pac arm had both sensitizing EGFR mutations exon 19 del and L858R. ^fOther includes patients with sensitizing EGFR mutations S768I, L861Q and G719X. ^gPrior lines were counted only when the reason for stopping was disease progression. ^hOne EGFR⁺ patient received EGFR TKI, but the reason for stopping was not disease progression. ⁱOne patient was wrongly randomized as EGFR WT in the interactive voice- or web-based response system and had received no prior TKI treatment. ^jIncludes one EGFR WT patient who received prior EGFR TKI.

Primary and secondary efficacy outcomes

At clinical cutoff (2 February 2023), the minimum and median follow-up durations were 10.5 and 14.0 months, respectively. A total of 239 PFS events occurred (Fig. 2a). Median investigator-assessed PFS (INV-PFS; primary outcome) was 9.5 months with ABCPEm/Pac and 7.1 months with BCPEm/Pac (stratified hazard ratio (HR): 0.84; 95% confidence interval (CI): 0.65, 1.09; $P = 0.184$) (Fig. 2a). Results from the sensitivity analysis were consistent with those from the primary analysis (Supplementary Table 2). Subgroup analyses of INV-PFS are presented in Fig. 2b. No difference in PFS was observed by PD-L1 status in the TC <1% (unstratified HR: 0.80; 95% CI: 0.56, 1.15), TC ≥1% (unstratified HR: 0.86; 95% CI: 0.60, 1.23), TC <50% (unstratified HR: 0.83; 95% CI: 0.62, 1.12) and TC ≥50% (unstratified HR: 0.90, 95% CI: 0.56, 1.46) subgroups. Unstratified HR for PFS comparing ABCPEm/Pac with BCPEm/Pac was 0.72 (95% CI: 0.52, 1.00) in male patients and 1.07 (95% CI: 0.71, 1.61) in female patients. Median INV-PFS was similar between the ABCPEm/Pac and BCPEm/Pac arms in the EGFR mutation subgroup (8.5 versus 8.3 months; unstratified HR: 0.86, 95% CI: 0.61, 1.21) and showed numerical differences in the wild-type (WT) subgroup (10.4 versus 7.0 months; unstratified HR: 0.81; 95% CI: 0.55, 1.19) (Extended Data Fig. 1a,b). In patients with tumors carrying EGFR mutations, INV-PFS improvement with ABCPEm/Pac versus BCPEm/Pac was generally similar across subgroups (Extended Data Fig. 1c). Median independent review facility-assessed PFS (IRF-PFS) was 9.5 months and 8.2 months in the ABCPEm/Pac and BCPEm/Pac arms, respectively (stratified HR: 0.88; 95% CI: 0.68, 1.15), consistent with INV-PFS (Extended Data Fig. 2).

OS was relatively immature with 49% events at clinical cutoff due to the short follow-up duration. Median OS was 20.7 months in the ABCPEm/Pac arm and 18.7 months in the BCPEm/Pac arm (stratified HR: 0.93; 95% CI: 0.67, 1.28) (Fig. 3a). OS was generally balanced between arms across key patient subgroups (Fig. 3b). No difference in OS was observed by level of PD-L1 expression or by sex. The unstratified HR of OS was 0.78 (95% CI: 0.49, 1.22) in the EGFR mutation subgroup and 1.11 (95% CI: 0.70, 1.75) in the WT subgroup (Extended Data Fig. 3a, b). In patients with tumors harboring EGFR mutations, OS improvement with ABCPEm/Pac versus BCPEm/Pac was generally similar across subgroups (Extended Data Fig. 3c).

Confirmed objective response rate (ORR) was 48% in the ABCPEm/Pac arm (73 of 152 patients) and 50% in the BCPEm/Pac arm (76 of 153 patients) (Extended Data Table 1). Confirmed complete response occurred in 0 and 1 (1%) of patients in the ABCPEm/Pac and BCPEm/Pac arms, respectively. In patients who had a confirmed response, median duration of response (DOR) was 11.3 months with ABCPEm/Pac and 8.3 months with BCPEm/Pac. ORR was similar in both treatment arms regardless of EGFR mutation status (Extended Data Table 2). DOR was 11.3 months with ABCPEm/Pac and 8.0 months with BCPEm/Pac in the EGFR mutation subgroup and 11.7 and 9.7 months, respectively, in the WT subgroup.

Follow-up anticancer treatment was administered to 79 of 152 patients (52%) in the ABCPEm/Pac arm and 101 of 153 patients (66%) in the BCPEm/Pac arm (Extended Data Table 3). In the EGFR mutation subgroup, 63% of patients receiving ABCPEm/Pac and 70% of patients receiving BCPEm/Pac underwent follow-up anticancer therapy. In the WT subgroup, 39% and 62% of patients receiving ABCPEm/Pac and BCPEm/Pac, respectively, underwent follow-up anticancer therapy. The most common follow-up anticancer treatment received in the EGFR mutation subgroup was targeted therapy (ABCPEm/Pac: 39 of 51 patients; BCPEm/Pac: 47 of 57 patients), whereas most patients in the WT subgroup received chemotherapy (ABCPEm/Pac: 18 of 28 patients; BCPEm/Pac: 31 of 44 patients).

Due to study termination in June 2024, updated OS data (in the ITT population and by EGFR mutation status) at the final data cut (data snapshot: 16 August 2024) were available, with an additional 18 months of follow up (Supplementary Data 1).

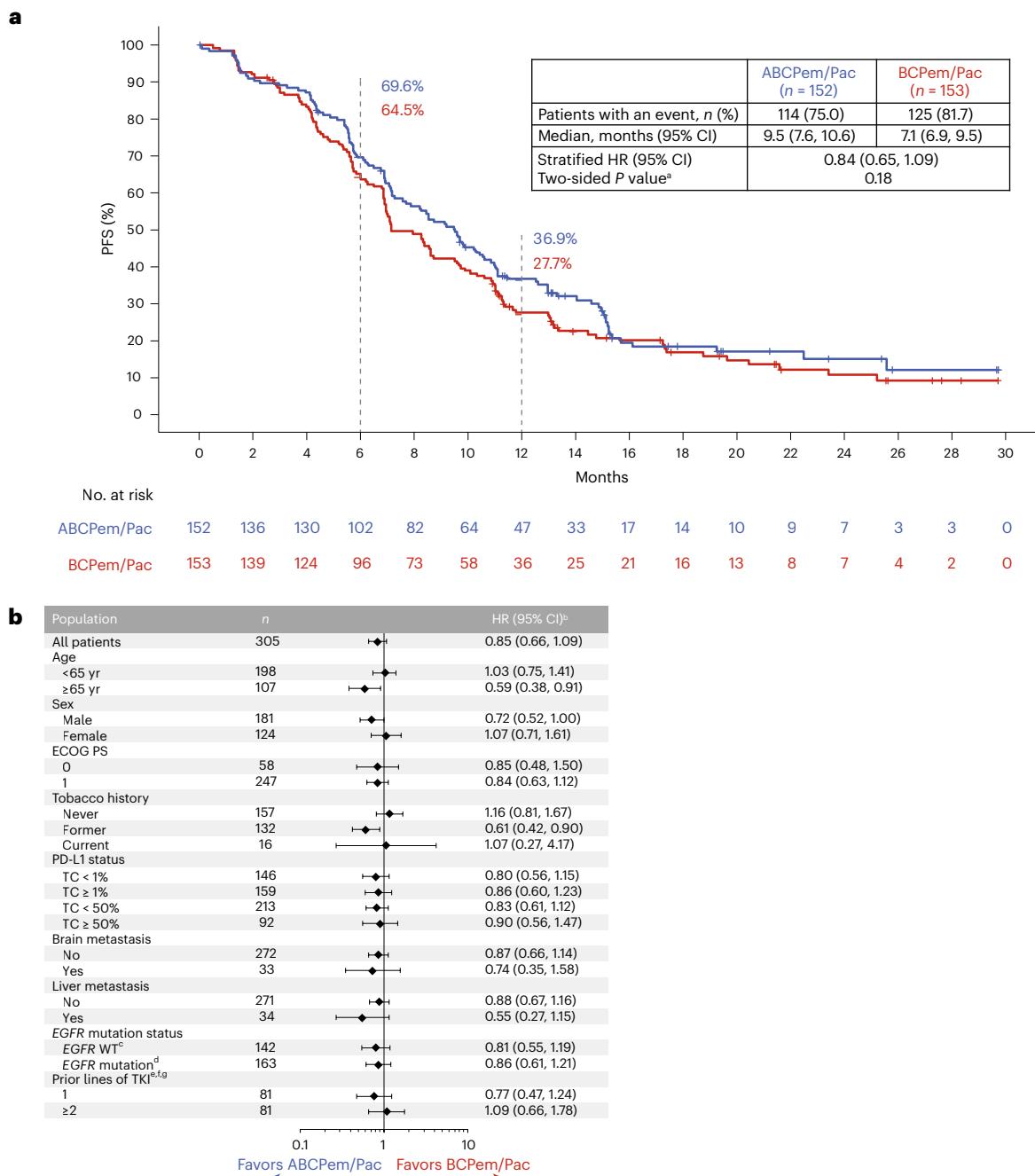


Fig. 2 | Investigator-assessed PFS. **a**, Kaplan-Meier curves in the ITT population. **b**, Forest plot in key patient subgroups. Data markers in **b** represent HRs, with error bars indicating 95% CIs. ^aStratified log-rank. ^bUnstratified HR is reported. ^cIncludes patients with ALK WT tumors. ^dIncludes patients with sensitizing EGFR mutations exon 19 del (n = 96); L858R (n = 57); S768I, L861Q and G719X (n = 7);

and ALK rearrangement (n = 5). ^ePrior lines were counted only when the reason for stopping was disease progression. ^fOne patient with EGFR mutation received EGFR TKI, but the reason for stopping was not disease progression. ^gOne patient was wrongly randomized as EGFR WT in the interactive voice- or web-based response system and had received no prior TKI treatment.

Safety

The safety-evaluable population was composed of 152 patients in the ABCPem/Pac arm and 153 patients in the BCPem/Pac arm (Table 2). At clinical cutoff, the median treatment duration was 7.6 months with atezolizumab, 6.3 months with bevacizumab, 2.1 months with carboplatin, 6.3 months with pemetrexed and 2.2 months with paclitaxel in the ABCPem/Pac arm. In patients receiving BCPem/Pac, the median treatment duration was 6.3 months with placebo, 6.1 months with bevacizumab, 2.1 months with carboplatin, 6.2 months with pemetrexed and 2.1 months with paclitaxel.

All-grade adverse events (AEs) occurred in 99% of patients receiving ABCPem/Pac (grades 3 and 4: 66%) and 100% of patients receiving BCPem/Pac (grades 3 and 4: 61%) (Table 2). The most common AEs in the ABCPem/Pac and BCPem/Pac arms were decreased neutrophil count (76% and 75%), anemia (75% and 76%) and decreased white blood cell count (61% and 62%) (Extended Data Table 4). AEs that led to discontinuation of any treatment were observed in 23% and 15% of patients receiving ABCPem/Pac and BCPem/Pac, respectively (Table 2). All-grade grade 5 AEs occurred in 8% of patients in the ABCPem/Pac arm (treatment related: 6%) and 8% of patients in the BCPem/Pac arm (treatment related: 7%).

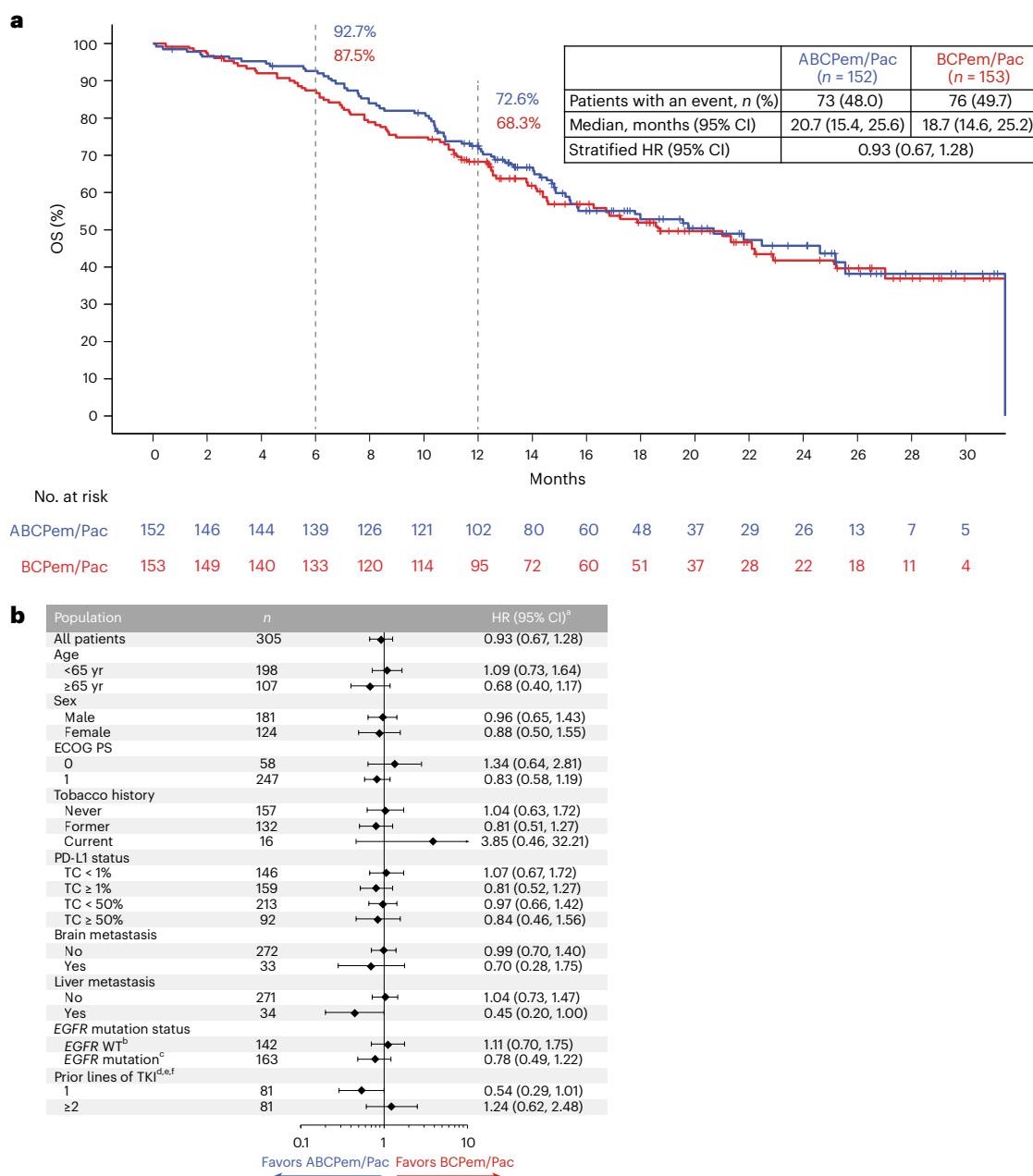


Fig. 3 | Overall survival. **a**, Kaplan–Meier curves in the ITT population. **b**, Forest plot of OS in key patient subgroups. Data markers in **b** represent HRs, with error bars indicating 95% CIs. ^aUnstratified HR is reported. ^bIncludes patients with ALK WT tumors. ^cIncludes patients with sensitizing EGFR mutations exon 19 del ($n=96$); L858R ($n=57$); S768I, L861Q and G719X ($n=7$); and ALK rearrangement ($n=5$). ^dPrior lines were counted only when the reason for stopping was disease progression. ^eOne patient with EGFR mutation received EGFR TKI, but the reason for stopping was not disease progression. ^fOne patient was wrongly randomized as EGFR WT in the interactive voice- or web-based response system and had received no prior TKI treatment.

($n=5$). ^dPrior lines were counted only when the reason for stopping was disease progression. ^eOne patient with EGFR mutation received EGFR TKI, but the reason for stopping was not disease progression. ^fOne patient was wrongly randomized as EGFR WT in the interactive voice- or web-based response system and had received no prior TKI treatment.

AEs of special interest (AESIs) for atezolizumab were observed in 68% (grades 3 and 4: 11%) and 71% (grades 3 and 4: 7%) of patients receiving ABCPem/Pac and BCPem/Pac, respectively. The most common AESIs for atezolizumab in the ABCPem/Pac and BCPem/Pac arms, respectively, were hepatitis (diagnosis and laboratory abnormalities: 55% and 59%), hypothyroidism (16% and 11%) and rash (13% and 8%) (Extended Data Table 5). The majority of AESIs under the medical concept of hepatitis (diagnosis and laboratory abnormalities) were hepatitis (laboratory abnormalities: 53% and 58%).

Exploratory biomarker analyses

The biomarker-evaluable population for RNA sequencing included 123 patients in the ABCPem/Pac arm and 127 patients in the BCPem/Pac arm

(Extended Data Table 6). Key demographics and baseline characteristics in the biomarker-evaluable population were generally similar across both treatment arms except for a numerically higher percentage of patients with brain metastasis in the BCPem/Pac arm.

RNA sequencing analysis showed that the EGFR mutation subgroup had statistically significant increased expression of genes involved in cell cycling and apoptosis (for example, *SMC1B* and *HSPB6*). The WT subgroup had statistically significant increased expression of effector T cell and natural killer (NK)-cell genes (for example, *NKG7* and *GZMB*) (Fig. 4a). Gene set enrichment analysis (GSEA) showed that genes in cell proliferation (for example, E2F targets and G2M checkpoint) and metabolism (for example, oxidative phosphorylation and fatty acid metabolism) were expressed at higher levels in the EGFR

Table 2 | Safety summary in the safety-evaluable population

<i>n</i> (%)	ABCPEm/Pac (n=152)	BCPEm/Pac (n=153)
All-grade AE, any cause	151 (99.3)	153 (100)
Grades 3 and 4 ^a	101 (66.4)	94 (61.4)
Grade 5	12 (7.9)	12 (7.8)
All-grade AE, treatment-related ^b	150 (98.7)	153 (100)
Grades 3 and 4 ^{a,c}	102 (67.1)	95 (62.1)
Grade 5	9 (5.9)	10 (6.5)
Serious AE	64 (42.1)	52 (34.0)
Treatment-related ^b	56 (36.8)	49 (32.0)
AE leading to withdrawal from any treatment	35 (23.0)	23 (15.0)
Atezolizumab	11 (7.2)	8 (5.2)
Bevacizumab	22 (14.5)	16 (10.5)
Atezolizumab AESI	103 (67.8)	109 (71.2)
Grades 3 and 4 ^a	17 (11.2)	11 (7.2)
Grade 5	2 (1.3)	1 (0.7)
Requiring use of systemic corticosteroid	28 (18.4)	15 (9.8)
Confirmed/suspected COVID-19	20 (13.2)	15 (9.8)

^aCounts in 'grades 3 and 4' are the number of patients whose highest grade of AEs are 3 or 4. ^bBased on investigator assessment of causality; related to any study drug. ^cPatients with unrelated grade 5 and related grades 3 and 4 AEs were included.

mutation subgroup, and genes in immune response (for example, TNF signaling and inflammatory response), tumor suppressor pathway (P53 pathway) and tumor suppressor–promoter dual role pathway (for example, lymphotoxin-alpha signaling) were enriched in the WT subgroup (Fig. 4b). Analysis of signatures that reflect the status of the tumor microenvironment showed a significantly lower level of effector T cells, NK cells, plasma cells and neutrophils, and a higher level of type-2 conventional dendritic cells and DNA damage response signature in the *EGFR* subgroup, indicating a colder immune status than in the WT subgroup (Fig. 4c).

In the ABCPEm/Pac arm, RNA sequencing analysis showed that long PFS (\geq median) was associated with statistically significant increased expression of genes involved in immune response (for example, *SFTPA1* and *HOPX*) and in IL2 signaling (for example, *CCL4* and *CD69*). Short PFS ($<$ median) was associated with statistically significant increased expression of genes involved in cell cycle and migration (for example, *COL7A1* and *KRT17*) and genes correlated with worse cancer prognosis (for example, *HASPIN* and *DEFB1*) (Extended Data Fig. 4a). In the BCPEm/Pac arm, RNA sequencing analysis showed that long PFS was associated with statistically significant increased expression of genes involved in immune response (for example, *SFTPA1* and *GLB1L3*) and in the inhibition of PI3K signaling (for example, *SLC34A2*). Short PFS was associated with statistically significant increased expression of genes involved in cell cycle and migration (for example, *COL7A1* and *KRT17*), and genes promoting cancer proliferation and invasion (for example, *ANXA8* and *L1CAM*) (Extended Data Fig. 4b). The association between hallmark pathway expression levels and PFS in each arm is shown in Extended Data Fig. 4c. Pathways that were differentially expressed in the *EGFR* mutation and WT subgroups and were associated with PFS in both the ABCPEm/Pac and BCPEm/Pac arms include E2F targets, G2M checkpoint, mitosis, oxidative phosphorylation, allograft rejection, inflammatory response, IL-6–JAK–STAT signaling and interferon- γ response. TNF and IL-2 pathways, which had lower gene expression levels in the *EGFR* mutation subgroup than in the WT subgroup, were correlated with long PFS in the ABCPEm/Pac arm only. These results could explain the numerically shorter median PFS between patients

receiving ABCPEm/Pac who have *EGFR*-mutant tumors versus WT tumors (Extended Data Fig. 1).

Tumor microenvironment signature analysis indicated that high gene expression levels of T cells, conventional dendritic cells, major histocompatibility complex II, tumor-associated macrophages and CD16-positive monocytes were correlated with long PFS in the ABCPEm/Pac arm (Extended Data Fig. 4d). Of note, macrophages and monocytes are typically considered as immunosuppressive cells. Expression of the abovementioned immune cell types were not associated with PFS in the BCPEm/Pac arm.

Post hoc analyses of the impact of the COVID-19 pandemic

At the clinical cutoff date, the coronavirus disease 2019 (COVID-19) pandemic was assessed by the sponsor to have had a minor impact on the primary analysis of IMpower151. The benefit–risk profile of ABCPEm/Pac and BCPEm/Pac could be conclusively established, as both efficacy and safety data were robust and interpretable.

Discussion

The approval of ABCPac for first-line treatment of metastatic nsqNSCLC with or without *EGFR* genomic alterations in the United States, the European Union and other regions has advanced the treatment landscape^{6,7}. However, the exact mechanisms behind differences between Asian and Western patients, as well as their impact on treatment response, remains to be elucidated. Here, we report findings from IMpower151, which was designed to address regional differences in patient genomic composition and clinical practice. IMpower151 did not meet its primary endpoint of INV-PFS in the ITT population. Additionally, in the ITT population, OS did not show clinically meaningful improvement with ABCPEm/Pac versus BCPEm/Pac at the primary analysis; OS results were relatively immature due to the short follow-up duration.

The results of the IMpower151 study are inconsistent with the significant PFS and OS improvements seen with ABCPac in IMpower150 (ref. 4). IMpower151 was conducted in China and all enrolled patients were Asian, whereas IMpower150 took place in 26 countries globally and 14% and 12% of patients in the ABCPac ($n = 400$) and BCPac ($n = 400$) arms, respectively, were Asian⁴. The percentage of patients who never smoked was 51% in IMpower151 and 20% in IMpower150 (ABCPac: 21%; BCPac: 19%)⁴. The percentage of patients who had tumors with *EGFR* mutations was 53% in IMpower151 and 14% in IMpower150 (ABCPac: 11%; BCPac: 16%)⁴. The prevalence of *EGFR* mutations in both studies is consistent with that reported in screening studies conducted in Asian and Caucasian populations with NSCLC^{10–12}. Almost all patients (97%) in IMpower151 received pemetrexed, and this is reflective of the clinical practice in China⁹. On the other hand, all patients in IMpower150 received paclitaxel per the study protocol⁴. Previous studies have shown greater PFS benefit with bevacizumab plus platinum-based chemotherapy plus pemetrexed than with bevacizumab plus platinum-based chemotherapy plus paclitaxel^{13,14}. It is, therefore, possible that the chemotherapy backbone has an impact on the efficacy of bevacizumab–chemotherapy combinations, potentially reducing the relative treatment effect observed with ABCPEm/Pac versus BCPEm/Pac in IMpower151. Additionally, the standard of care for TKI treatment was different during the periods when the studies were conducted. When IMpower150 was ongoing (March 2015 to December 2016), the standard-of-care first-line therapy for patients with *EGFR* plus NSCLC was first- and second-generation TKIs. By the time IMpower151 was initiated in 2020, the treatment paradigm for *EGFR*⁺ metastatic nsqNSCLC had shifted from first- and second-generation to third-generation TKIs (for example, osimertinib^{15,16}). In addition, a higher proportion of patients enrolled in IMpower151 had received ≥ 2 lines of TKI therapy than in IMpower150. Notably, 66% of patients with tumors carrying *EGFR* mutations in IMpower151 had received a third-generation TKI. These factors could contribute to the PFS and OS results observed when atezolizumab was added to bevacizumab plus chemotherapy in IMpower151.

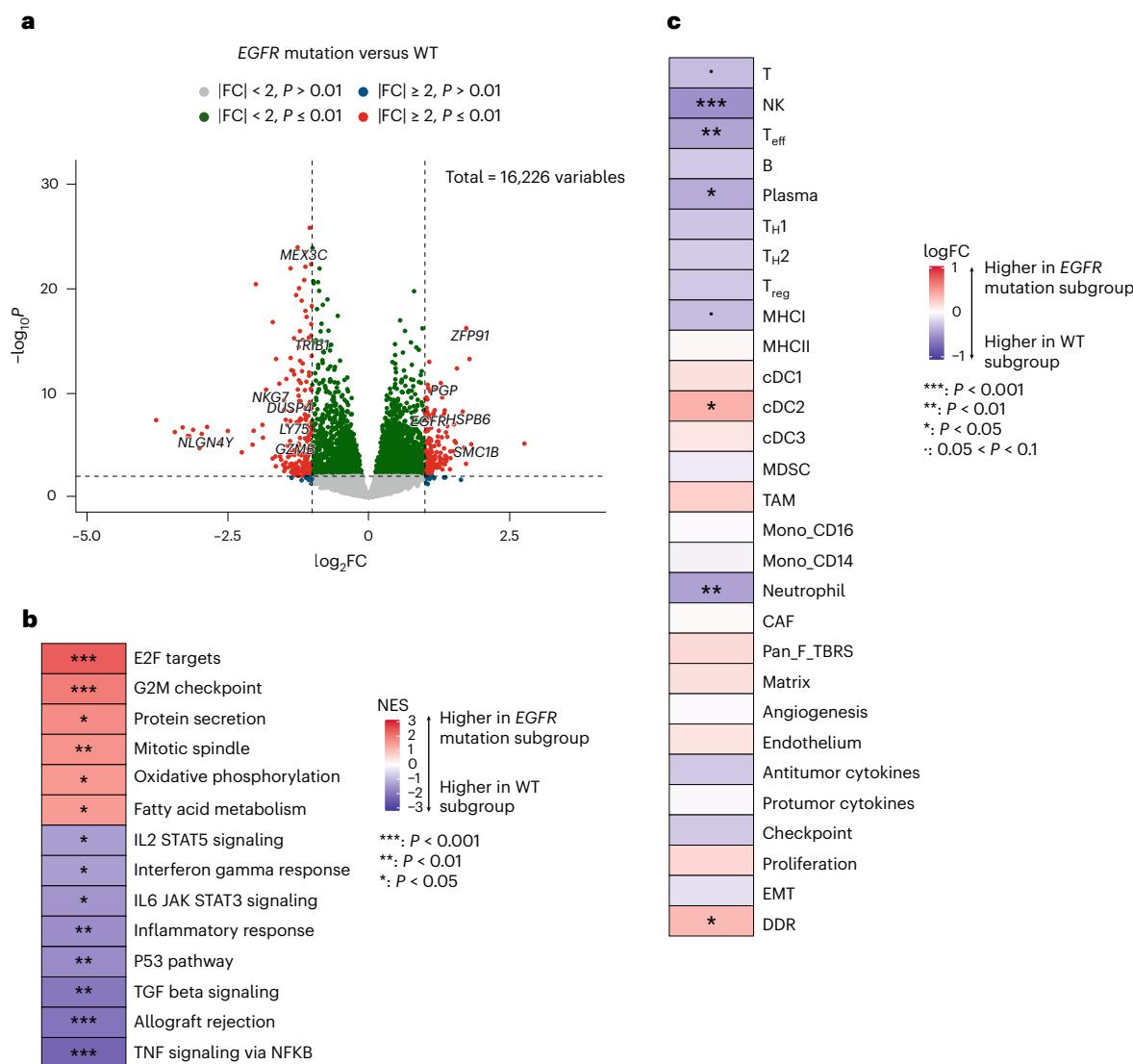


Fig. 4 | RNA sequencing comparison of the EGFR mutation subgroup versus the WT subgroup. **a**, Volcano plot of differentially expressed genes. The log₂FC indicates the fold change in the expression level for each gene. Each dot represents one gene. |FC| of 2 and unadjusted P value of 0.01 were used to define genes that are differentially expressed at statistically significant levels. Genes that were significantly up or down regulated were labeled in red. **b**, Hallmark analysis of differentially expressed genes. The enriched gene sets in the EGFR mutation and WT subgroups were labeled in red and blue, respectively. Asterisks denote the level of statistical significance. **c**, Gene expression signature analysis. The gene signatures that are expressed at higher levels in the EGFR mutation and

WT subgroups were labeled in red and blue, respectively. Asterisks denote the level of statistical significance. All P values reported are two sided. The CAMERA method was used to adjust P values in **b** and **c** to account for multiple hypothesis testing. CAF, cancer-associated fibroblast; cDC, conventional dendritic cell; DDR, DNA damage response; EMT, epithelial-to-mesenchymal transition; FC, fold change; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; Mono_CD14, CD14⁺ monocytes; Mono_CD16, CD16⁺ monocytes; NES, normalized enrichment score; Pan_F_TBRS, pan-fibroblast TGF-β response signature; TAM, tumor-associated macrophages; T_{eff}, effector T cell; T_{H1}, T helper 1 cell; T_{H2}, T helper 2 cell; T_{reg}, regulatory T cell.

The subsequent anticancer therapy may also have affected OS results. Regardless of EGFR mutation status, a higher percentage of patients in the BCPem/Pac arm received follow-up targeted therapy and chemotherapy compared with the ABCPem/Pac arm. In the WT subgroup, a higher percentage of patients in the BCPem/Pac arm than ABCPem/Pac arm received follow-up anticancer therapy across various therapy categories; the largest difference between both arms was seen with subsequent immunotherapy. This discrepancy seen in the WT subgroup could be attributed to the availability of standard-of-care therapies as the next line of treatment after treatment discontinuation. Consequently, the OS benefit with ABCPem/Pac versus BCPem/Pac in the WT subgroup could potentially be reduced, contributing to a diminished OS benefit in the ITT population.

Overall, findings in the EGFR mutation subgroup were consistent with those of other prospective phase 3 studies that investigated the combination of immune checkpoint inhibitors and chemotherapy in a similar patient population (that is, patients with tumors harboring EGFR mutations post TKI failure)^{17,18}. The KEYNOTE-789 study did not meet both its co-primary endpoints of PFS and OS with pembrolizumab plus chemotherapy versus placebo plus chemotherapy¹⁸. Similarly, the CheckMate 722 study also did not meet its primary endpoint of PFS with nivolumab plus chemotherapy versus chemotherapy alone¹⁷. However, in CheckMate 722, there was a trend favoring nivolumab plus chemotherapy over chemotherapy in patients with tumors carrying EGFR-sensitizing mutations, one line of previous EGFR TKI or both¹⁸. These observations were not found in IMpower151, which could be due to the limited size of the subgroups. Nonetheless, IMpower151 is one of a few

prospective phase 3 studies investigating the combination of immune checkpoint inhibitors and chemotherapy in patients with tumors carrying *EGFR* mutations, adding further insight to the management of this population and the development of new clinical trial designs.

Although the IMpower151 study lacks significant positive findings, other studies investigating the combination of immunotherapy with anti-vascular endothelial growth factor (VEGF) plus chemotherapy have shown treatment benefit in Chinese patients with EGFR-mutant metastatic nsqNSCLC whose disease had progressed after EGFR-TKI treatment^{19,20}. In the second interim analysis of the phase 3 ORIENT-31 study, prolonged PFS was demonstrated with the combination of sintilimab (PD-1 inhibitor) and IBI305 (a bevacizumab biosimilar) plus chemotherapy compared with chemotherapy (HR: 0.51; 95% CI: 0.39, 0.67)¹⁹. Similar PFS benefit was also seen with sintilimab plus chemotherapy versus chemotherapy alone (HR: 0.72; 95% CI: 0.55, 0.94). No significant OS benefit was seen with the sintilimab-IBI305-chemotherapy combination (HR: 0.98; 95% CI: 0.72, 1.34) nor with sintilimab plus chemotherapy (HR: 0.97; 95% CI: 0.71, 1.32) versus chemotherapy alone. In the first interim analysis of the HARMONI-A study, ivonescimab (anti-PD-1/VEGF bispecific antibody) in combination with chemotherapy significantly prolonged PFS versus placebo plus chemotherapy (HR: 0.46; 95% CI: 0.34, 0.62)²⁰. Most patients (>85%) had received prior third-generation EGFR-TKI treatment. Unlike IMpower151, neither of these studies included anti-VEGF in the control arm. Further investigation is needed to confirm if the benefit attributed by anti-VEGF outweighs that by immunotherapy in this setting.

In IMpower150 and other studies in NSCLC, greater survival benefit with immune checkpoint inhibitors was seen in male than in female patients^{5,21}. However, due to the small sample size of the subgroups by sex in IMpower151, such interpretations of data should be made with caution.

Exploratory biomarker analyses were performed to understand the association of these markers with study treatment response. RNA sequencing analysis of gene signatures in the tumor microenvironment indicated a colder immune status in the *EGFR* mutation subgroup compared with the WT subgroup. In the ABCPem/Pac arm, but not in the BCPem/Pac arm, elevated gene signatures of T cells, dendritic cells and major histocompatibility complex, as well as myeloid families, were associated with prolonged PFS. The presence of immunosuppressive tumor-associated myeloid cells (TAMCs), such as macrophages and myeloid-derived suppressor cells^{22,23}, has been strongly correlated with CD8⁺ T cell exhaustion and correlated with poor immuno-oncology treatment efficacy in multiple disease settings^{24–26}. In the phase 2 IMmotion150 study of renal cell carcinoma, less PFS benefit with atezolizumab monotherapy was seen in patients with high effector T cell and high myeloid cell gene expression than in patients with high effector T cell and low myeloid cell gene expression²⁷. However, patients with high effector T cell and high myeloid cell gene expression showed better PFS with atezolizumab plus bevacizumab than with atezolizumab alone²⁷. The improved PFS seen with the addition of bevacizumab to atezolizumab in this subgroup may be due to the blockade of VEGF or VEGF receptor, which led to the reduction of myeloid-derived suppressor cells in the tumor microenvironment, as shown in other research on preclinical tumor models and human cancers^{28–30}. TAMCs play complex roles in antitumor immunity, with different subsets having opposing effects due to heterogeneity of TAMCs. For example, in our RNA sequencing analysis, CD16⁺ monocyte signatures correlated with longer PFS, potentially through NK cell recruitment that could be further activated by atezolizumab³¹. On the other hand, CD14⁺ monocyte signatures were not correlated with longer PFS as CD14⁺ monocytes may promote cancer via the mechanisms that atezolizumab and bevacizumab could not inhibit effectively, including remodeling extracellular matrix and differentiating into immune suppressive tumor-associated macrophages^{32,33}. Further investigations into the underlying mechanisms are needed to shed light on new therapeutic

strategies and biomarker development. Results from our biomarker analysis also showed that tumor-promoting hallmark gene sets in lung cancer and other cancer types, but not any immune signatures, were associated with shorter PFS in the ABCPem/Pac arm but not in the BCPem/Pac arm. Findings from these exploratory analyses are limited by the small sample size and warrant further investigation in other cohorts of tumor tissues and in blood samples to validate these results and evaluate the potential clinical value of RNA biomarkers. Notably, analytical, bioinformatic and regulatory challenges exist for using RNA sequencing to select or stratify patients in clinical trials. Hence, it is critical to establish benchmark standards, optimize assays for clinical conditions and demonstrate assay reproducibility. Future work may also focus on utilizing RNA sequencing findings to identify biomarkers that can be detected on diagnostic platforms that are more clinically developed, such as polymerase chain reaction, immunohistochemistry or NanoString.

ABCPem/Pac was generally well tolerated, with no new safety signals identified. In IMpower151, all-grade AESIs were predominantly due to the medical concept of hepatitis, which included both hepatitis (diagnosis) and hepatitis (laboratory abnormalities; for example, increased alanine transaminase and increased aspartate transaminase). The majority of these hepatitis AESIs were laboratory abnormalities, which occurred at higher rates than in IMpower150 (ABCP: 12%; BCP: 7%)⁴. Most of the AESIs in IMpower151 were low grade, and the ≥grade 3 AESI rates were comparable to those in IMpower150 (ref. 4).

Limitations of this study include the small sample size, lack of statistical power to detect the desired effect size in subgroups by baseline characteristics (including *EGFR* mutation and sex) and the small sample sizes in the exploratory biomarker subgroup analyses. A small number of patients (*n* = 11) had TKI treatments between sampling and randomization, which could have altered their tumor PD-L1 level, *EGFR* mutation status and RNA sequencing expressions. Another limitation is that the study was conducted during COVID-19, resulting in COVID-19 related AEs, protocol deviations and missing tumor assessments. However, sensitivity analysis to account for missing data showed similar PFS results as the primary analysis, indicating minimal impact of the pandemic on the primary endpoint. In addition, self-selection bias or other biases in the recruitment process was minimized by ensuring that the study sites reflected a good geographical representation of the diverse patient population in China and by using a central interactive voice- and web-response system for patient identification and treatment assignment.

Despite not meeting its primary endpoint, IMpower151 provided insights on the efficacy and safety of ABCPem/Pac versus BCPem/Pac in patients with nsqNSCLC in China, where baseline demographics and clinical practices are different from those in global studies. This study highlights the need for more efforts to elucidate the mechanisms behind the differences in epidemiologic characteristics between Asian and Western patients with lung cancer.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-025-03658-y>.

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Methods

Study design and patient population

IMpower151 (ClinicalTrials.gov, NCT04194203) was conducted according to the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. Approval of the protocols was obtained from independent review boards or ethics committees at each study site, and from regulatory authorities per local requirements (Supplementary Table 1). All patients provided written informed consent. All relevant requirements by China's Ministry of Science and Technology related to the export of genetic information and materials for this work have been fulfilled.

IMpower151 is a phase 3, randomized, multicenter, double-blind study investigating bevacizumab, carboplatin and investigator's choice of either pemetrexed or paclitaxel in combination with atezolizumab (ABC-Pem/Pac) or placebo (BCPem/Pac) in the first-line treatment of metastatic nsqNSCLC. Patients aged ≥ 18 years with stage IV nsqNSCLC who had not received prior treatment or systemic therapy in the metastatic nsq setting (adjuvant or neoadjuvant chemotherapy, radiotherapy or chemoradiotherapy was permitted if the duration between the last treatment administration and the date of randomization was ≥ 6 months) and who had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and ECOG PS of 0 or 1 were enrolled by investigators at clinical sites in China (Supplementary Table 1). Patients needed to have a representative tumor sample that could be evaluated for prospective central testing of PD-L1 TC expression (SP263 PD-L1 immunohistochemical assay; Ventana Medical Systems) and the presence of EGFR mutations and ALK gene rearrangements. Recruitment of patients to the WT subgroup was limited to 50% of the sample size to reflect the natural prevalence in the Chinese population with advanced nsqNSCLC^{10,11}. Patients with sensitizing EGFR mutations or ALK gene rearrangements must have experienced disease progression (during or after treatment) or were intolerant to treatment with one or more TKIs that were appropriate for the treatment of EGFR-mutant NSCLC. Patients were excluded if life expectancy was less than 3 months or if there was evidence of bleeding diathesis or coagulopathy, tumor invasion or abutting of major blood vessels. The study design only considered the sex of the patients, which was self-reported. The full protocol can be accessed in the Supplementary Information.

Procedures and interventions

For eligible patients, the study site obtained the patient's identification number and treatment assignment from a central interactive voice- and web-response system to minimize self-selection bias. Enrolled patients were randomized 1:1 to the ABC-Pem/Pac or BCPem/Pac arms using a stratified block method (block size of four). Patients received 21-day cycles of atezolizumab or placebo (1,200 mg) plus bevacizumab (15 mg per kg), carboplatin (area under the concentration curve 6 mg per ml per min) and paclitaxel (175 mg per m²) or pemetrexed (500 mg per m²) intravenously for four cycles, followed by atezolizumab or placebo maintenance treatment until unacceptable toxicity or loss of clinical benefit, and bevacizumab and pemetrexed (if given during induction) until progression per RECIST v.1.1. The use of paclitaxel or pemetrexed was determined by the investigator and documented before randomization and was not permitted to be changed during the study. Randomization was stratified by genotype of EGFR or ALK gene (genomic alterations versus WT) and PD-L1 expression (TC < 50% versus TC $\geq 50\%$ by the SP263 immunohistochemistry assay).

Study site personnel and patients were blinded to treatment assignment during the study. The sponsor and its agents were also blinded to treatment assignment, except for individuals who required access to fulfill their job roles during a clinical trial. Unblinding was permitted for medical emergencies and for select non-medical emergencies, such as at the time of unequivocal disease progression by

RECIST v.1.1 and study treatment discontinuation to help guide decisions on subsequent treatment, provided conditions in the protocol were met.

Study endpoints and assessments

The primary endpoint was INV-PFS (defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurred first) per RECIST v.1.1 in the ITT population. Secondary endpoints included INV-PFS by EGFR mutation and PD-L1 status, IRF-PFS in the ITT population, OS (defined as the time from randomization to death from any cause) in the ITT population, ORR (defined as the proportion of patients with a complete or partial response on two consecutive occasions ≥ 4 weeks apart as determined by the investigator per RECIST v.1.1) and DOR (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurred first, as determined by the investigator per RECIST v.1.1). ORR was analyzed in all randomized patients with measurable disease at baseline. DOR was assessed in patients with a complete or partial response on two consecutive occasions ≥ 4 weeks apart as determined by the investigator per RECIST v.1.1.

Exploratory objectives included INV-PFS rate at 6 months and 1 year, and OS rate at 1 and 2 years. Patients underwent tumor assessments during screening, every 6 weeks from day 1 of cycle 1 for the first 12 months, and every 9 weeks thereafter until the occurrence of disease progression per RECIST v.1.1 (loss of clinical benefit among patients who continued to receive treatment after disease progression), withdrawal of consent, death or study termination by the sponsor, whichever occurred first.

Exploratory biomarker objectives included OS by EGFR mutation and PD-L1 status, ORR and DOR by EGFR mutation status, and RNA sequencing analyses of hallmark pathways and gene signatures by EGFR mutation status and PFS (\geq median or $<$ median). The biomarker-evaluable population included patients with available tumor tissue samples and evaluable data for PD-L1 status, EGFR mutation status and RNA sequencing analyses. For RNA sequencing analyses, RNA sequencing data had to meet criteria on depth and correlation on the principal component analysis plot.

Safety objectives were to evaluate the incidence, nature and severity of AEs or AESIs suggesting an autoimmune cause, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v.5.0). The safety-evaluable population was defined as all randomized patients who received any amount of any component of study treatment.

Statistical analyses

IMpower151 was planned to randomize approximately 306 patients, assuming a 1:1 randomization ratio, one-sided significance level of 0.025, a dropout (no further data on disease progression status and survival can be collected during the study period) rate of 5% per 12 months for PFS, 90% power to detect an HR of 0.65 (corresponding to an improvement in median PFS from 6.8 to 10.5 months in the ITT population) and exponentially distributed event times. The final PFS analysis was to be conducted when approximately 227 PFS events in the ITT population had occurred or ≥ 10 months after the last patient was enrolled, whichever occurs last. This event number would allow for a minimum detectable difference corresponding to an HR of approximately 0.77 in the ITT population. The recruitment period was anticipated to be approximately 20 months, and the final PFS analysis was expected to occur approximately 30 months after the first patient was randomized.

Kaplan–Meier methodology was used to estimate median PFS and OS for each treatment arm. HRs were estimated using a stratified Cox regression model, using the same stratification factors that were used during randomization. The Brookmeyer–Crowley methodology was

used to calculate the 95% CIs³⁴. All subgroup analyses presented were unstratified due to the small sample size and their exploratory nature.

The estimate of ORR and its 95% CI was calculated using the Clopper–Pearson method. ORR was compared between the two treatment arms using the stratified Mantel–Haenszel test and 95% CIs were determined using the normal approximation to the binomial distribution. Formal hypothesis testing will not be performed for DOR, and comparisons between treatment arms will be made for descriptive purposes.

No data were excluded from analyses. For missing PFS data, patients without a date of disease progression were analyzed as censored observations on the date of the last tumor assessment. Missing OS data from patients who were not reported as having died were censored on the date they were last known to be alive. If no post-baseline tumor assessment was available, PFS and OS were censored at the date of randomization.

For missing ORR data, patients without any post-baseline assessment were considered nonresponders. Missing DOR data for patients who had not progressed and who had not died at the time of analysis were censored at the time of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR was censored at the date of the first occurrence of a complete or partial response.

Baseline characteristics of the ITT and biomarker-evaluable populations, safety data and information on follow-up anticancer treatment were summarized. Sensitivity analysis was conducted based on interval censoring to evaluate the impact of missed or delayed tumor assessments on INV-PFS (Supplementary Methods 1). Data from case report forms were collected using Medidata Classic Rave (v.2022.3.2) and non-case report form data (including IxRS and laboratory data) were obtained using the Edison Platform (pRED Informatics, F. Hoffmann-La Roche Ltd). Statistical analyses were conducted using SAS (v.9.4). The full statistical analysis plan can be accessed in the Supplementary Information.

RNA sequencing

Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) samples using the AllPure FFPE DNA/RNA Kit (Magen Biotechnology Co., Ltd) and quantified using the Qubit RNA High Sensitivity Assay (Thermo Fisher Scientific Inc.). RNA quality was assessed using the Qsep100 Bio-Fragment Analyzer (BiOptic Inc.) and RNA cartridge. RNA sequencing was performed using the TruSeq RNA Access Library Prep Kit (Illumina, Inc. (cat. no. RS-301-2001 and RS-301-2002); PCR primer cocktail was included in the kit). RNA sequencing reads were first aligned to ribosomal RNA sequences to remove ribosomal reads. The remaining reads were then aligned to the human reference genome (NCBI Build 38) using GSNAP v.2013-11-01. The number of reads mapped to the exons of each gene was calculated using the R/Bioconductor package GenomicAlignments to quantify gene expression levels. Raw counts for genes were normalized by trimmed mean of *M*-values based on size factors as calculated using CalcNormFactors in the edgeR package. Trimmed mean of *M*-values-normalized counts were subsequently voom transformed using the voom function in the R package limma, resulting in normalized log₂ (counts per million (CPM)-mapped reads) data. Genes with low expressions were filtered out if the summarized gene expressions were less than 0.5 CPM in the smallest comparison subgroup. All RNA sequencing measurements were taken from distinct sets of FFPE tumor tissue slides and were only measured once due to the limitation of number of slides. Only one set of FFPE tumor tissue slides was collected from each patient who provided these samples.

Differential gene expression was performed using the R package limma, comparing patients with tumors carrying *EGFR* mutations and patients with WT tumors, or between patients with long and short PFS. Volcano plots for these analyses were plotted using the EnhancedVolcano R package. Significant differential gene expression was defined as an absolute log₂ fold-change of ≥ 1 and unadjusted *P* ≤ 0.05 . Gene signature scores were calculated for each sample as the arithmetic

mean of log₂ (CPM) expression of all genes in a given signature, which included the Hallmark gene set collection from the MSigDB database and the other signatures from internal and public literatures. GSEA was performed using the fgsea package v.1.14.0. and the signatures using a differential expression linear model as the input. The CAMERA method was used to adjust *P* values to account for multiple hypothesis testing. All RNA sequencing analyses were conducted in R (v.4.0.3).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

For eligible studies, qualified researchers can request access to individual-patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Individual-patient-level RNA sequencing data are made available to qualified researchers at the European Genome-phenome Archive platform. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification. Datasets from clinical trials including RNA sequencing can be requested after August 2026 per Roche's Policy (18 months after completion of clinical study report). The data sharing shall also comply with applicable local regulations. Gene signatures were included from the Hallmark gene set collection from the MSigDB database and from internal and public literatures. Source data are provided with this paper.

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Acknowledgements

We thank the patients who participated in the trial, the patients' families and the investigators and staff at all clinical study sites. The IMpower151 study was sponsored by F. Hoffmann-La Roche, Ltd. The funder had a role in study design, data collection, data analysis, data interpretation and writing of the report. Medical writing assistance for this manuscript was provided by B. Lim, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche, Ltd.

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Conceptualization: C.Z., C.S., M.B. and M.K.S. Methodology: C.Z., I.Y., X.H. and C.S. Software: X.H. Formal analysis: C.Z., I.Y., X.H. and M.K. Investigation: C.Z., X.D., Zhehai Wang, X.W., Y.Y., Y.C., H.P., X.Z., J. Cui, L.W., X.L., Ziping Wang, Q. Wang, J.H., M.W., C.S. and M.B. Resources: C.Z., X.D., Zhehai Wang, X.W., Y.Y., Y.C., H.P., X.Z., L.W., X.L., Ziping Wang, J.H., M.W. and M.B. Data curation: X.H. and C.S. Writing—original draft: I.Y. and C.S. Writing—review and editing: all authors. Visualization: X.H. and C.Z. Supervision: C.Z. and M.B. Project administration: C.Z., X.D., Y.Y., H.P., X.Z., L.W., Ziping Wang, J.H. and M.W.

Competing interests

C.Z. received honoraria as a speaker/consultant from Alice, Amoy Diagnostics, AnHeart, Boehringer Ingelheim, C-Stone, Eli Lilly China, Hengrui, Innovent Biologics, LUYE Pharma, Merck Sharp & Dohme, Qilu, Roche, Sanofi and TopAlliance Biosciences Inc. along with advisor fees from Hengrui, Innovent Biologics, Qilu and TopAlliance Biosciences Inc. C.Z. declares non-financial competing interests as the IASLC President-Elect. I.Y., M.X., X.H., J. Cai and Q.Wu are employees of Roche (China) Holding Ltd and own stocks from Roche. L.Q. and C.S. are employees of Roche (China) Holding Ltd. M.B., M.K., M.K.S. are

employees of Genentech and own stocks from Roche. The other authors declare no competing interests.

Additional information

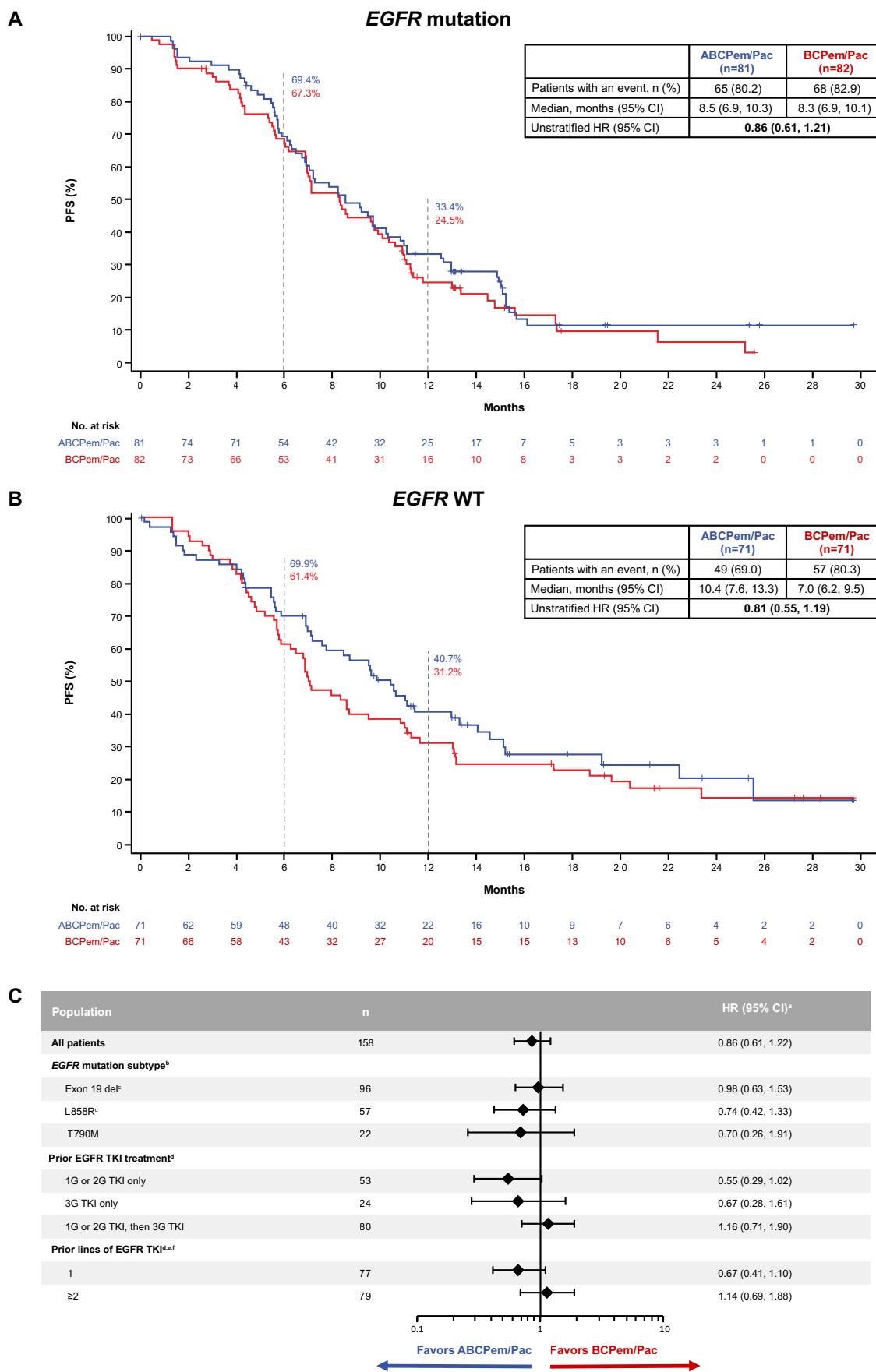
Extended data is available for this paper at
<https://doi.org/10.1038/s41591-025-03658-y>.

Supplementary information The online version contains supplementary material available at
<https://doi.org/10.1038/s41591-025-03658-y>.

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Peer review information *Nature Medicine* thanks Gregory A. Masters, Giorgio Scagliotti, Ming Wang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Liam Messin, in collaboration with the *Nature Medicine* team.

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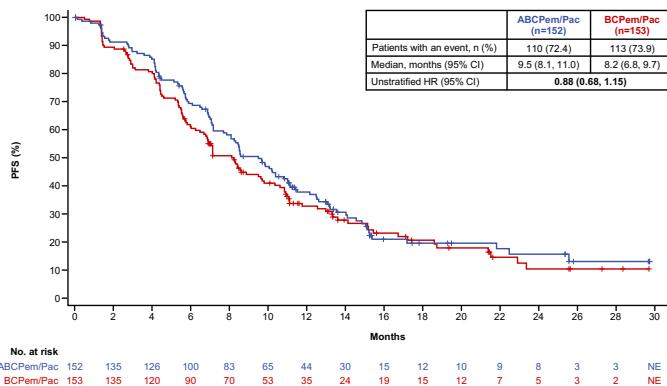
Extended Data Fig. 1 | See next page for caption.

Extended Data Fig. 1 | Investigator-assessed PFS by EGFR mutation status.

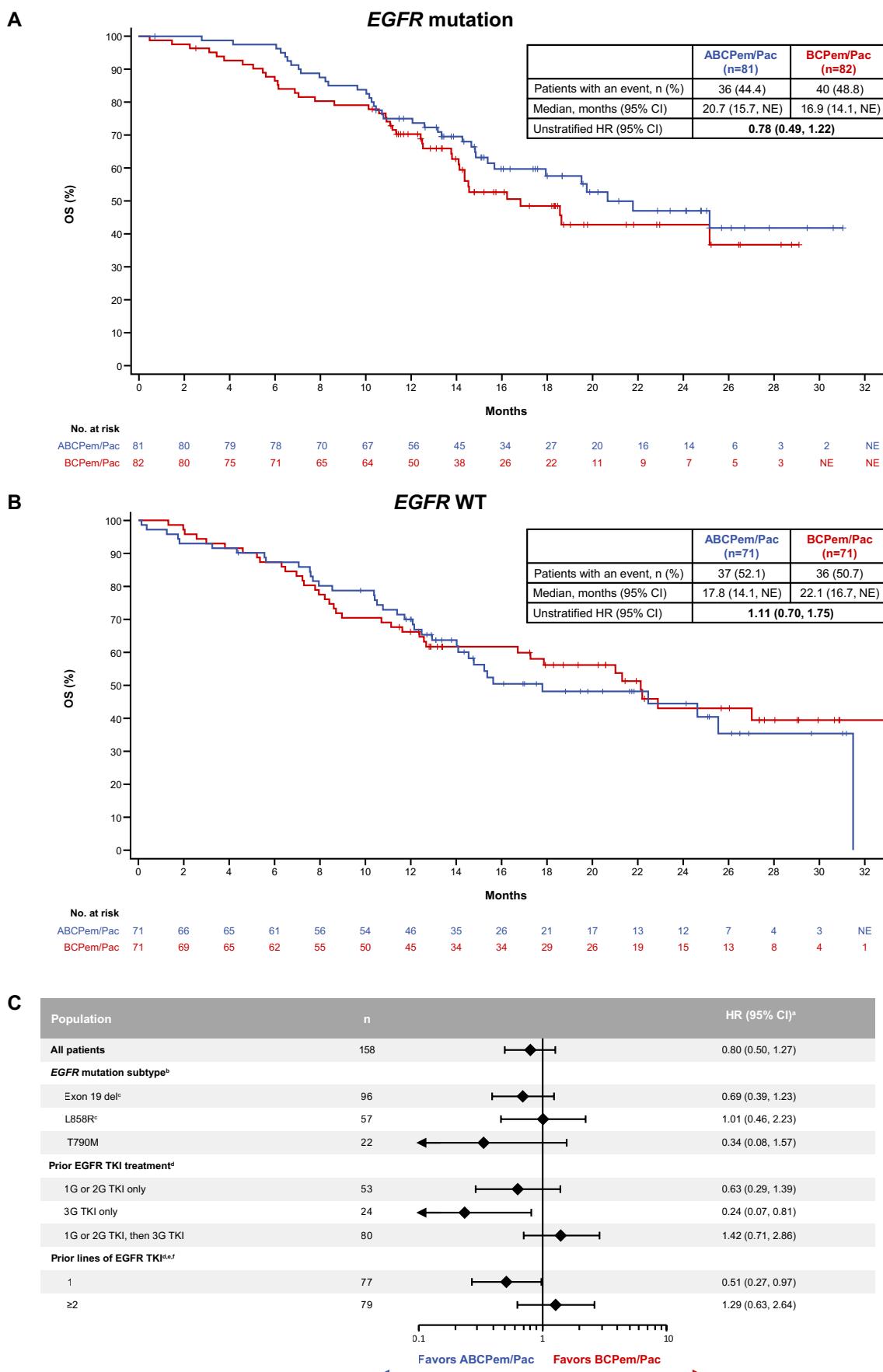
Kaplan-Meier curves in patients with (a) *EGFR* mutation and (b) *EGFR* WT. *EGFR* mutation status was based on the presence of *EGFR* genomic alterations or *ALK* rearrangements. Sensitizing *EGFR* mutations include exon 19 del, L858R, S768I, L861Q, and G719X. (c) Investigator-assessed PFS in key patient subgroups of the *EGFR* mutation group. Data markers in (c) represent HRs, with error bars indicating 95% CIs. ^a Unstratified HR is reported. ^b Includes patients with sensitizing *EGFR* mutations S768I, L861Q and G719X (n = 7). ^c Two patients in the ABCPem/Pac arm had both sensitizing *EGFR* mutations exon19 del and L858R.

^d One patient was wrongly randomized as *EGFR* WT in the interactive voice- or

web-based response system and had received no prior TKI treatment. ^e Prior lines were counted only when the reason for stopping was disease progression. ^f One patient with *EGFR* mutation received EGFR TKI but the reason for stopping was not disease progression. 1G, first generation; 2G, second generation; 3G, third generation; ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; *ALK*, anaplastic large-cell lymphoma kinase; ABCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; TKI, tyrosine kinase inhibitor; WT, wild type.



Extended Data Fig. 2 | IRF-assessed PFS. Kaplan-Meier curves in the intention-to-treat population. ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CI, confidence interval; HR, hazard ratio; IRF, independent review facility.

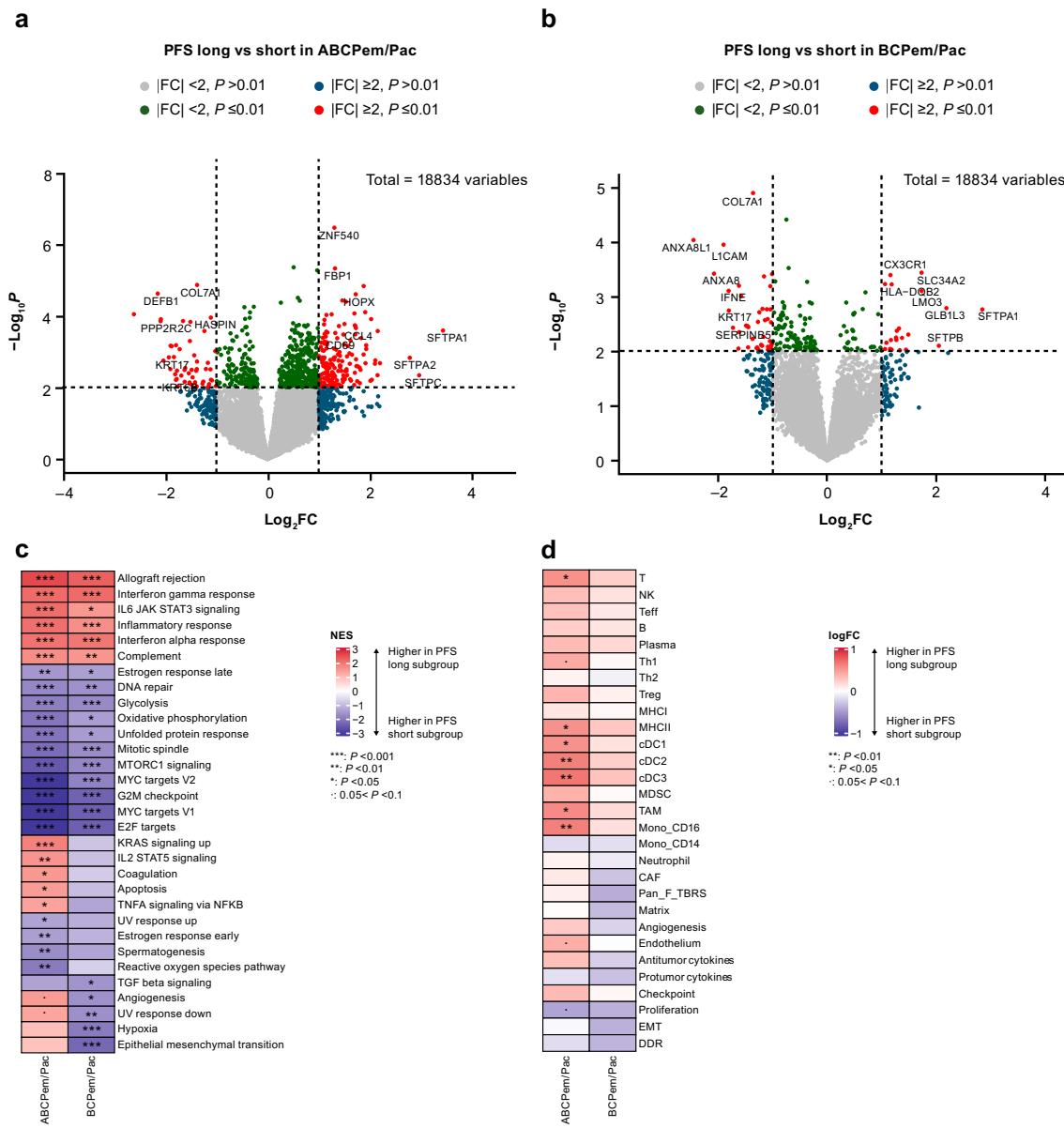


Extended Data Fig. 3 | See next page for caption.

Extended Data Fig. 3 | OS by EGFR mutation status. Kaplan-Meier curves in patients with (a) *EGFR* mutation and (b) *EGFR* WT. *EGFR* mutation status was based on the presence of *EGFR* genomic alterations or *ALK* rearrangements. Sensitizing *EGFR* mutations include exon 19 del, L858R, S768I, L861Q, and G719X. (c) OS in key patient subgroups of the *EGFR* mutation group. Data markers in (c) represent HRs, with error bars indicating 95% CIs. ^aUnstratified HR is reported. ^bIncludes patients with sensitizing *EGFR* mutations S768I, L861Q and G719X (n = 7). ^cTwo patients in the ABCPem/Pac arm had both sensitizing *EGFR* mutations exon19 del and L858R.

^dOne patient was wrongly randomized as *EGFR* WT in the interactive voice- or

web-based response system and had received no prior TKI treatment. ^ePrior lines were counted only when the reason for stopping was disease progression. ^fOne patient with *EGFR* mutation received EGFR TKI but the reason for stopping was not disease progression. 1G, first generation; 2G, second generation; 3G, third generation; ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; *ALK*, anaplastic large-cell lymphoma kinase; ABCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; NE, not estimable; TKI, tyrosine kinase inhibitor; WT, wild type.



Extended Data Fig. 4 | RNA sequencing comparison of patients with long PFS (\geq median) vs short PFS ($<$ median) in the ITT population. (a) Volcano plot of differentially expressed genes in the ABCPem/Pac arm. The \log_2 FC indicates the fold change in the expression level for each gene. Each dot represents one gene. $|FC| \geq 2$ and unadjusted P value of 0.01 were used to define genes that are differentially expressed at statistically significant levels. Genes that were significantly up or down regulated were labeled in red. (b) Volcano plot of differentially expressed genes in the BCpem/Pac arm. The \log_2 FC indicates the fold-change in the expression level for each gene. Each dot represents one gene. $|FC| \geq 2$ and unadjusted P value of 0.01 were used to define genes that are differentially expressed at statistically significant levels. Genes that were significantly up or down regulated were labeled in red. (c) Hallmark analysis of differential gene expression in the ABCPem/Pac and BCpem/Pac arms. The enriched gene sets in the long and short PFS subgroups were labeled in red and blue, respectively, for both the ABCPem/Pac and BCpem/Pac arms. Asterisks denote the level of statistical significance. (d) Gene expression signature analysis

in the ABCPem/Pac and BCpem/Pac arms. The gene signatures that are expressed at higher levels in the long and short PFS subgroups were labeled in red and blue, respectively, for both the ABCPem/Pac and BCpem/Pac arms. Asterisks denote the level of statistical significance. All P values reported are 2 sided. The CAMERA method was used to adjust P values in (c) and (d) to account for multiple hypothesis testing. ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; BCpem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CAF, cancer-associated fibroblast; cDC, conventional dendritic cell; DDR, DNA damage response; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; FC, fold change; ITT, intention to treat; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; Mono_CD14, CD14⁺ monocytes; Mono_CD16, CD16⁺ monocytes; NES, normalized enrichment score; Pan_F_TBRS, pan-fibroblast TGF- β response signature; PFS, progression-free survival; TAM, tumor-associated macrophages; T_{eff}, effector T cell; T_{H1}, T helper 1 cell; T_{H2}, T helper 2 cell; T_{reg}, regulatory T cell; WT, wild type.

Extended Data Table 1 | Confirmed ORR and DOR in the intention-to-treat population

	ABCPem/Pac (n=152)	BCPem/Pac (n=153)
ORR, n (%)	73 (48.0)	76 (49.7)
Complete response	0	1 (0.7)
Partial response	73 (48.0)	75 (49.0)
Stable disease	60 (39.5)	61 (39.9)
Disease progression	10 (6.6)	9 (5.9)
DOR		
Responders, n	73	76
Responders with subsequent event, n (%)	47 (64.4)	60 (78.9)
Median, months (95% CI)	11.3 (7.4, 13.6)	8.3 (5.7, 9.9)

ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CI, confidence interval; DOR, duration of response; ORR, objective response rate.

Extended Data Table 2 | Confirmed ORR and DOR by EGFR mutation status

	EGFR mutation		WT	
	ABCPem/Pac (n=81)	BCPem/Pac (n=82)	ABCPem/Pac (n=71)	BCPem/Pac (n=71)
ORR, n (%)	34 (42.0)	41 (50.0)	39 (54.9)	35 (49.3)
95% CI	31.1, 53.5	38.7, 61.3	42.7, 66.8	37.2, 61.4
DOR				
Responders, n (%)	34 (42.0)	41 (50.0)	39 (54.9)	35 (49.3)
Responders with subsequent event, n (%)	24 (70.6)	34 (82.9)	23 (59.0)	26 (74.3)
Median, months (95% CI)	11.3 (7.6, 13.8)	8.0 (5.7, 9.7)	11.7 (6.7, 17.8)	9.7 (5.6, 15.9)

EGFR mutation status was based on the presence of EGFR genomic alterations or ALK rearrangements.

ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; ALK, anaplastic large-cell lymphoma kinase; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; CI, confidence interval; DOR, duration of response; EGFR, epidermal growth factor receptor; ORR, objective response rate; WT, wild type.

Extended Data Table 3 | Follow-up anticancer treatment by *EGFR* mutation status

n (%)	<i>EGFR</i> mutation		WT	
	ABCPem/Pac (n=81)	BCPem/Pac (n=82)	ABCPem/Pac (n=71)	BCPem/Pac (n=71)
Patients with at least one treatment	51 (63.0)	57 (69.5)	28 (39.4)	44 (62.0)
Targeted therapy	39 (48.1)	47 (57.3)	14 (19.7)	22 (31.0)
3G EGFR TKI				
Osimertinib	9 (11.1)	9 (11.0)	0	0
Aumolertinib	6 (7.4)	4 (4.9)	1 (1.4)	0
Furmonertinib	5 (6.2)	1 (1.2)	1 (1.4)	0
Lazertinib	0	1 (1.2)	0	0
2G EGFR TKI				
Dacomitinib	4 (4.9)	0	0	0
Afatinib	2 (2.5)	4 (4.9)	0	1 (1.4)
1G EGFR TKI				
Erlotinib	0	1 (1.2)	0	0
Gefitinib	3 (3.7)	0	0	0
ALK TKI				
Alectinib	0	1 (1.2)	0	0
Lorlatinib	0	1 (1.2)	0	0
Anti-VEGF therapies				
Catequentinib	11 (13.6)	15 (18.3)	9 (12.7)	11 (15.5)
Bevacizumab	8 (9.9)	12 (14.6)	3 (4.2)	4 (5.6)
Endostatin	2 (2.5)	0	0	0
Famitinib	0	0	1 (1.4)	1 (1.4)
Rivoceranib	0	0	0	2 (2.8)
Other targeted therapies ^a	7 (8.6)	6 (7.3)	2 (2.8)	9 (12.7)
Antibody-drug conjugates	1 (1.2)	0	0	1 (1.4)
Chemotherapy, n (%)	25 (30.9)	34 (41.5)	18 (25.4)	31 (43.7)
Immunotherapy, n (%)	14 (17.3)	13 (15.9)	10 (14.1)	24 (33.8)
Other therapies, n (%)	7 (8.6)	3 (3.7)	5 (7.0)	10 (14.1)
EGFR mutation status was based on the presence of EGFR genomic alterations or ALK rearrangements.				
1G, first generation; 2G, second generation; 3G, third generation; ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; ALK, anaplastic large-cell lymphoma kinase; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand-1; TC, tumor cell; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; WT, wild type. ^a Other targeted therapies include adagrasib, amivantamab, capmatinib, flumatinib, fluzoparib, GFH925, palbociclib, patritumab, pralsetinib, pyrotinib, rituximab, savolitinib, trastuzumab, investigational antineoplastic drugs, other monoclonal antibodies and antibody drug conjugates, antineoplastic monoclonal antibodies, and protein kinase inhibitors.				

Extended Data Table 4 | AEs in ≥20% of patients in either arm in the safety-evaluable population

n (%)	ABC Pem/Pac (n=152)	BC Pem/Pac (n=153)
Neutrophil count decreased	115 (75.7)	114 (74.5)
Anemia	114 (75.0)	117 (76.5)
White blood cell count decreased	92 (60.5)	95 (62.1)
Platelet count decreased	81 (53.3)	89 (58.2)
Proteinuria	66 (43.4)	51 (33.3)
Decreased appetite	56 (36.8)	54 (35.3)
Aspartate aminotransferase increased	55 (36.2)	69 (45.1)
Nausea	55 (36.2)	46 (30.1)
Constipation	52 (34.2)	54 (35.3)
Alanine aminotransferase increased	45 (29.6)	59 (38.6)
Hypoalbuminemia	42 (27.6)	28 (18.3)
Weight decreased	36 (23.7)	29 (19.0)
Hypertension	30 (19.7)	38 (24.8)
ABC Pem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; AE, adverse event; BC Pem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel.		

Extended Data Table 5 | AESIs for atezolizumab in the safety-evaluable population by grade

n (%)	ABCPem/Pac (n=152)		BCPem/Pac (n=153)	
	All grade	Grade 3-4	All grade	Grade 3-4
Any AESI for atezolizumab	103 (67.8) ^a	17 (11.2)	109 (71.2) ^a	11 (7.2)
Hepatitis (diagnosis and laboratory abnormalities)	84 (55.3) ^a	13 (8.6)	91 (59.5)	9 (5.9)
Hepatitis (laboratory abnormalities)	80 (52.6) ^a	10 (6.6)	89 (58.2)	8 (5.2)
Hepatitis (diagnosis)	10 (6.6) ^a	4 (2.6)	3 (2.0)	1 (0.7)
Hypothyroidism	25 (16.4)	0	17 (11.1)	0
Rash	20 (13.2)	1 (0.7)	13 (8.5)	0
Infusion-related reactions	11 (7.2)	1 (0.7)	6 (3.9)	0
Pneumonitis	5 (3.3)	0	6 (3.9) ^a	1 (0.7)
Myocarditis	2 (1.3)	1 (0.7)	0	0
Hyperthyroidism	2 (1.3)	0	1 (0.7)	0
Nephritis	2 (1.3)	0	1 (0.7)	0
Pancreatitis	2 (1.3)	0	1 (0.7)	0
Colitis	1 (0.7)	1 (0.7)	0	0
Severe cutaneous reactions	1 (0.7)	1 (0.7)	0	0
Adrenal insufficiency	1 (0.7)	0	1 (0.7)	0
Diabetes mellitus	0	0	2 (1.3)	1 (0.7)
Guillain-Barre syndrome	0	0	1 (0.7)	0

ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; AESI, adverse event of special interest; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel. ^a Grade 5 events reported (one case each for ascites, hepatic failure, and interstitial lung disease).

Extended Data Table 6 | Baseline characteristics in the RNA sequencing biomarker-evaluable population

	Biomarker-evaluable population		<i>EGFR</i> mutation ^a		<i>EGFR</i> WT	
	ABCPem/Pac (n=123)	BCPem/Pac (n=127)	ABCPem/Pac (n=64)	BCPem/Pac (n=64)	ABCPem/Pac (n=57)	BCPem/Pac (n=60)
Median age, years	60	61	60	61	60	62
Sex, male, n (%)	75 (61.0)	77 (60.6)	27 (42.2)	32 (50.0)	47 (82.5)	44 (73.3)
ECOG PS 1, n (%)	103 (83.7)	105 (82.7)	58 (90.6)	57 (89.1)	43 (75.4)	45 (75.0)
Never smoker, n (%)	65 (52.8)	64 (50.4)	46 (71.9)	40 (62.5)	18 (31.6)	22 (36.7)
Liver metastasis, n (%)	13 (10.6)	14 (11.0)	5 (7.8)	8 (12.5)	7 (12.3)	6 (10.0)
Brain metastasis, n (%)	10 (8.1)	18 (14.2)	7 (10.9)	10 (15.6)	2 (3.5)	6 (10.0)
Bone metastasis, n (%)	59 (48.0)	63 (49.6)	31 (48.4)	39 (60.9)	26 (45.6)	23 (38.3)
SLD at baseline, median, mm	51.0	47.0	41.6	37.5	63.0	61.6
ABCPem/Pac, atezolizumab plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; BCPem/Pac, placebo plus bevacizumab, carboplatin, and pemetrexed or paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; <i>EGFR</i> , epidermal growth factor receptor; SLD, sum of longest diameter; WT, wild type. ^a Includes patients with sensitizing <i>EGFR</i> mutations exon 19 del, L858R, S768I, L861Q, and G719X.						

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Data collection Case report form data: Medidata Classic Rave® 2022.3.2
Non-case report form data: Edison Platform - © 2025 F. Hoffmann-La Roche Ltd.

Data analysis Statistical analyses for clinical data: SAS (version 9.4)
RNA sequencing analyses: R (version 4.0.3); R package limma and EnhancedVolcano R package

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For eligible studies, qualified researchers can request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (<https://vivli.org/ourmember/roche/>). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to

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Reporting on sex and gender

The study design only considered the sex of the patients, which was self-reported. No difference in OS was observed by level of PD-L1 expression or by sex.

Reporting on race, ethnicity, or other socially relevant groupings

This study was conducted in China. No socially relevant groupings were used.

Population characteristics

The median age was 61 years (range, 30–76). Fifty-nine percent of the patients were male, 51% never smoked, and 81% had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. PD-L1 expression status was TC $\geq 1\%$ and TC $\geq 50\%$ in 52% and 30% of patients, respectively, and EGFR mutations were detected in 53% of patients. Approximately 97% of patients were selected by their investigator to receive pemetrexed. Eighty-one of 162 patients (50%) received ≥ 2 prior lines of EGFR or ALK TKI treatment. Of 157 patients who received prior EGFR TKI treatment, 66% received a third-generation TKI.

Recruitment

IMpower151 was conducted according to the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. Self-selection bias or other biases in the recruitment process was minimized by ensuring that the study sites reflected a good geographical representation of the diverse patient population in China and by using a central interactive voice- and web-response system for patient identification and treatment assignment.

Ethics oversight

Approval of the protocols was obtained from independent review boards or ethics committees at each study site, and from regulatory authorities per local requirements (Supplementary Table S1).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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Sample size

IMpower151 was planned to randomize approximately 306 patients, assuming a 1:1 randomization ratio, one-sided significance level of 0.025, a dropout (no further data on disease progression status and survival can be collected during the study period) rate of 5% per 12 months for PFS, 90% power to detect an HR of 0.65 (corresponding to an improvement in median PFS from 6.8 to 10.5 months in the ITT population), and exponentially distributed event times.

Data exclusions

No data were excluded from the analyses.

Replication

All RNA sequencing measurements were taken from distinct sets of FFPE tumor tissue slides and were only measured once due to the limitation of number of slides. Only one set of FFPE tumor tissue slides was collected from each patient who provided these samples.

Randomization

Enrolled patients were randomized 1:1 to the ABCPem/Pac or BCPem/Pac arms using a stratified block method (block size of 4). As pre-specified in the protocol and agreed by the local health authority, randomization generally ensures a balance of baseline covariates across treatment groups. Adjusting for additional variables may introduce overfitting in this moderately-sized trial.

Blinding

Study site personnel and patients were blinded to treatment assignment during the study. The Sponsor and its agents were also blinded to treatment assignment, except for individuals who required access to fulfil their job roles during a clinical trial. Unblinding was permitted for medical emergencies and for select non-medical emergencies, such as at the time of unequivocal disease progression by RECIST v1.1 and study treatment discontinuation to help guide decisions on subsequent treatment, provided conditions in the protocol are met.

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Clinical trial registration [ClinicalTrials.gov](#), NCT02366143

Study protocol The full protocol can be accessed in the Supplementary Materials.

Data collection From April 9, 2020, to March 18, 2022, 305 patients (ITT population) of 626 screened were enrolled in IMpower151 at 24 sites in China and randomized to the ABCPem/Pac (n=152) and BCPem/Pac (n=153) arms (Fig. 1 and Supplementary Table S1). Clinical cutoff was February 2, 2023.

Outcomes The primary endpoint was INV-PFS (defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first) per RECIST v1.1 in the ITT population. Secondary endpoints included INV-PFS by EGFR mutation and PD-L1 status, IRF-PFS in the ITT population, OS (defined as the time from randomization to death from any cause) in the ITT population, ORR (defined as the proportion of patients with a complete or partial response on two consecutive occasions ≥ 4 weeks apart as determined by the investigator per RECIST v1.1), and DOR (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1). ORR was analyzed in all randomized patients with measurable disease at baseline. DOR was assessed in patients with a complete or partial response on two consecutive occasions ≥ 4 weeks apart as determined by the investigator per RECIST v1.1.

Kaplan-Meier methodology was used to estimate median PFS and OS for each treatment arm. HRs were estimated using a stratified Cox regression model, using the same stratification factors that were used during randomization. The Brookmeyer-Crowley methodology was used to calculate the 95% CIs. All subgroup analyses presented were unstratified due to the small sample size and their exploratory nature.

The estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method. ORR was compared between the two treatment arms using the stratified Mantel-Haenszel test and 95% CIs were determined using the normal approximation to the binomial distribution. Formal hypothesis testing will not be performed for DOR, and comparisons between treatment arms will be made for descriptive purposes.

Plants

Seed stocks Not applicable

Novel plant genotypes Not applicable

Authentication Not applicable