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ORIGINAL ARTICLE

Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial

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Background: IMpower010 (NCT02486718) demonstrated significantly improved disease-free survival (DFS) with adjuvant atezolizumab versus best supportive care (BSC) following platinum-based chemotherapy in the programmed death-ligand 1 (PD-L1)-positive and all stage II-IIIA non-small-cell lung cancer (NSCLC) populations, at the DFS interim analysis. Results of the first interim analysis of overall survival (OS) are reported here.

Patient and methods: The design, participants, and primary-endpoint DFS outcomes have been reported for this phase III, open-label, 1 : 1 randomised study of atezolizumab (1200 mg q3w; 16 cycles) versus BSC after adjuvant platinum-based chemotherapy (1-4 cycles) in adults with completely resected stage IB (≥4 cm)-IIIA NSCLC (per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system, 7th edition). Key secondary endpoints included OS in the stage IB-IIIA intent-to-treat (ITT) population and safety in randomised treated patients. The first pre-specified interim analysis of OS was conducted after 251 deaths in the ITT population. Exploratory analyses included OS by baseline PD-L1 expression level (SP263 assay).

Results: At a median of 45.3 months' follow-up on 18 April 2022, 127 of 507 patients (25%) in the atezolizumab arm and 124 of 498 (24.9%) in the BSC arm had died. The median OS in the ITT population was not estimable; the stratified hazard ratio (HR) was 0.995 [95% confidence interval (CI) 0.78-1.28]. The stratified OS HRs (95% CI) were 0.95 (0.74-1.24) in the stage II-IIIA ($n = 882$), 0.71 (0.49-1.03) in the stage II-IIIA PD-L1 tumour cell (TC) ≥1% ($n = 476$), and 0.43 (95% CI 0.24-0.78) in the stage II-IIIA PD-L1 TC ≥50% ($n = 229$) populations. Atezolizumab-related adverse event incidences remained unchanged since the previous analysis [grade 3/4 in 53 (10.7%) and grade 5 in 4 (0.8%) of 495 patients, respectively].

Conclusions: Although OS remains immature for the ITT population, these data indicate a positive trend favouring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-L1 TC ≥50% stage II-IIIA subgroup. No new safety signals were observed after 13 months' additional follow-up. Together, these findings support the positive benefit–risk profile of adjuvant atezolizumab in this setting.

Key words: IMpower010, atezolizumab, NSCLC

INTRODUCTION

The recommended treatment for patients with early-stage resectable non-small-cell lung cancer (NSCLC) is surgery, which has been associated with 5-year survival rates ranging from 41% in those with stage IIIA NSCLC to 92% in those with stage IA1 disease.[1] To improve these outcomes, adjuvant therapy is given to treat micrometastatic disease and prevent recurrence.[2] Adjuvant cisplatin-based doublet chemotherapy became the standard of care for resected early-stage NSCLC in 2004.[3] The 5-year survival rates with adjuvant chemotherapy are 4%-5% higher than with observation,[3-5] leaving an unmet need for improvement.

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In patients with *EGFR* mutations, osimertinib is now the standard-of-care adjuvant therapy, as monotherapy or after adjuvant chemotherapy.[6,7] Immune checkpoint inhibitors have also transformed the treatment landscape of advanced NSCLC by demonstrating improved survival with manageable toxicity as monotherapy[8-10] and in combination with chemotherapy.[11,12] Subsequently, interest has turned to evaluating the safety and efficacy of immunotherapy in neoadjuvant and adjuvant settings in patients with resectable early-stage NSCLC.[2]

IMpower010 (NCT02486718) was the first phase III immunotherapy study to demonstrate a statistically significant disease-free survival (DFS) benefit with adjuvant atezolizumab versus best supportive care (BSC) in resected NSCLC following platinum-based chemotherapy.[13] In patients with stage II-IIIA NSCLC whose tumours expressed programmed death-ligand 1 (PD-L1) on ≥1% of tumour cells (PD-L1 TC ≥1%), the hazard ratio (HR) for DFS was 0.66 [95% confidence interval (CI) 0.50-0.88]. The greatest magnitude of DFS improvement was seen in patients with PD-L1 TC ≥50% stage II-IIIA NSCLC, in whom a 57% reduction in the risk of recurrence or death was observed with adjuvant atezolizumab versus BSC (DFS HR 0.43; 95% CI 0.27-0.68). DFS benefit was consistent across most patient demographic and disease subgroups within this population. Based on these findings, atezolizumab was approved as adjuvant treatment following platinum-based chemotherapy for patients with completely resected stage II-IIIA NSCLC with PD-L1 TC ≥1% in the United States, China, Japan, and other countries; patients with PD-L1 TC ≥50% stage II-IIIA NSCLC in the UK, Canada, Switzerland, Australia, Singapore, Uruguay, and Paraguay; and patients with PD-L1 TC ≥50% stage II-IIIA NSCLC excluding *EGFR* and *ALK* alterations in the European Union at the time of writing.

Although DFS endpoints are reached more quickly, overall survival (OS) is still an important endpoint for establishing clinical benefit in early-stage trials.[14] At the DFS interim analysis, OS, a key secondary endpoint of IMpower010, was not mature after a median of 32 months of follow-up with an event-to-patient ratio of 19%.[13] We report the outcomes of the first pre-specified interim analysis of OS and safety updates at the clinical cut-off of 18 April 2022, after a further 13 months of median follow-up.

PATIENTS AND METHODS

Study design and participants

The study design and participants in this randomised, multicentre, open-label, phase III study of adjuvant atezolizumab versus BSC following adjuvant platinum-based chemotherapy have been previously described.[13]

Briefly, eligible patients aged ≥18 years had completely resected stage IB (tumours ≥4 cm)-IIIA NSCLC (as per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system, seventh edition) and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients whose NSCLC had *EGFR* mutations and *ALK* rearrangements were also eligible.

During the first (enrolment) phase, all patients received adjuvant platinum-based chemotherapy following an anatomic NSCLC resection with negative margins. Thereafter, patients without disease recurrence who had completed 1-4 cycles of cisplatin-based chemotherapy and still met the eligibility criteria were randomised to receive atezolizumab or BSC during the randomised evaluation phase.

The study protocol and full eligibility criteria can be found in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2023.07.001. The protocol was approved by an institutional review board or an independent ethics committee at each study site. All patients provided written informed consent.

Randomisation and masking

Patients were identified for enrolment by the study investigators (see Collaborators in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2023.07.001.). Those eligible for the randomisation phase were assigned 1 : 1 using a permuted-block method with a block size of four to receive either atezolizumab or BSC using an interactive voice-web response system. Randomisation was stratified by sex, NSCLC stage, histology, and PD-L1 expression level.[13]

The treatment was open label, so masking was not required.

Procedures

During the enrolment phase, patients were given the investigators' choice of up to four 21-day cycles of the following chemotherapy regimens within 28-84 days after surgery: cisplatin 75 mg/m^2 intravenously on day 1 of each cycle plus either vinorelbine 30 mg/m^2 intravenously on days 1 and 8, docetaxel 75 mg/m^2 intravenously on day 1, gemcitabine 1250 mg/m^2 intravenously on days 1 and 8, or, for patients with non-squamous NSCLC, pemetrexed 500 mg/m^2 intravenously on day 1.

During the randomised evaluation phase, patients received either 16 cycles of atezolizumab 1200 mg every 3 weeks for ≤16 cycles or BSC, which included observation and regular scans for disease recurrence.

All patients underwent computed tomography assessment of the chest and upper abdomen at baseline, every 4 months for the first year, and every 6 months for the second year. Patients without disease recurrence continued disease status assessments with alternating chest computed tomography and X-ray every 6 months during years 3-5 and annually by X-ray thereafter.

Evaluation of PD-L1 TC expression by the SP263 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ) and *EGFR* mutation and *ALK* rearrangement status have been previously described.[13]

All adverse events were recorded throughout both study phases and for 30 days after the last dose of atezolizumab or the last study assessment in the BSC arm (90 days for serious and immune-mediated adverse events, with no time limit for events related to study treatment) or until the

initiation of another anticancer therapy, whichever occurred first. From 21 January 2021 until this interim analysis cut-off on 18 April 2022, only treatment-related serious adverse events and adverse events of special interest (AESIs) were to be reported.

Outcomes

The primary endpoint of investigator-assessed DFS has been previously reported.[13]

Key secondary endpoints included OS (defined as the time from the date of randomisation to death by any cause) in the intention-to-treat (ITT) population of patients with stage IB-IIIA NSCLC, defined as all randomised patients. Safety outcomes were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

The protocol specified four interim and one final OS analysis. The interim analyses of DFS and OS were conducted at different times due to different event accrual times. An exploratory OS analysis was conducted at the time of the DFS interim analysis on 21 January 2021, and the results were previously reported.[13] The first pre-specified OS interim analysis and an updated safety analysis were conducted at the clinical cut-off of 18 April 2022, and the results are presented here. The DFS data were not updated at this cut-off because the protocol specified only one interim DFS analysis.

Statistical analysis

A protocol amendment related to DFS analysis of PD-L1 subpopulations was previously reported.[13] In brief, until 29 June 2016, the study protocol included DFS analysis irrespective of PD-L1 expression and in patients with stage II-IIIA disease whose tumours had PD-L1 expression defined as TC2/3 or tumour-infiltrating immune cell (IC) 2/3 as per the SP142 assay (Ventana Medical Systems). On 11 February 2020, the PD-L1 population to be analysed for DFS was amended to patients with stage II-IIIA disease whose tumours expressed PD-L1 on $\geq$1% of TC as per the SP263 assay.

The planned sample size and pre-specified hierarchical statistical plan for testing the primary and key secondary endpoints were previously described.[13] Briefly, DFS and then OS were tested in different study populations in the following order: (i) DFS in patients with stage II-IIIA NSCLC whose tumours expressed PD-L1 on $\geq$1% of TC (referred to as the stage II-IIIA PD-L1 TC $\geq$1% population); (ii) DFS in all patients with stage II-IIIA NSCLC; (iii) DFS in the ITT population; and (iv) OS in the ITT population.[13] OS in the ITT population would only be tested when the DFS in the ITT population reached a statistically significant difference between treatment arms. At the previously reported interim analysis of DFS at the 21 January 2021 cut-off, the DFS difference between treatment arms was statistically significant in the stage II-IIIA PD-L1 TC $\geq$1% and stage II-IIIA populations but did not reach statistical significance in the ITT population, hence OS was not formally tested in the ITT population.[13] If DFS reaches statistical significance in the ITT population at the DFS final analysis, then OS will be formally tested in the ITT population at the pre-specified OS interim and final analyses. The first pre-specified interim analysis of OS was planned when $\sim$254 deaths had occurred in the ITT population, based on the α spending function with a one-sided α of 0.001.

Patients whose death had not been reported at the date of analysis were censored at the date when they were last known to be alive. If no post-baseline data were available, patients were censored at the date of randomisation plus 1 day.

Pre-specified exploratory analyses of OS at this clinical cut-off (18 April 2022) included OS in the stage II-IIIA and stage II-IIIA PD-L1 TC $\geq$1% populations and survival rates at 3 years from randomisation. *Post hoc* exploratory analyses of OS in the stage II-IIIA PD-L1 TC $\geq$50%, stage II-IIIA PD-L1 TC 1%-49%, and stage II-IIIA PD-L1 TC $<$1% populations were also conducted.

The median OS in each treatment arm was estimated using Kaplan—Meier methodology with two-sided 95% CIs calculated using the Brookmeyer—Crowley method. HRs were estimated using stratified (by sex, NSCLC stage, histology, and PD-L1 expression level) and unstratified Cox regression models, including two-sided 95% CIs. *P* values are shown for descriptive purposes only.

In subgroup analyses, unstratified HRs for survival were estimated from Cox proportional hazards models and Kaplan—Meier estimates of median survival time for each level of the categorical variables. OS rates 3 years from randomisation were estimated using Kaplan—Meier methodology for each treatment arm, along with 95% CIs calculated using Greenwood's formula.

Safety was analysed in the safety population (defined as all randomised patients who received at least one dose of atezolizumab or BSC), and adverse events were summarised by treatment arm.

Statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC).

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

RESULTS

A total of 1280 patients enrolled after resection between 7 October 2015 and 19 September 2018 (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.07.001). The ITT population comprised 1005 patients with stage IB-IIIA NSCLC [672 (66.9%) male] who were randomly assigned to receive atezolizumab ($n = 507$) or BSC ($n = 498$). The stage II-IIIA population included 442 patients in the atezolizumab arm and 440 in the BSC arm; the stage II-IIIA PD-L1 TC $\geq$1% population included 248 and 228 patients in the respective treatment arms, and the stage II-IIIA PD-L1 TC $\geq$50% population had 115 and 114 patients in the respective arms. On 18 April 2022 (cut-off), 161 patients

(31.8%) in the atezolizumab arm and 169 (33.9%) in the BSC arm had discontinued the study (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.07.001). The most common reasons for study discontinuation were death [122 patients (24.1% and 24.5%) in each arm] and patient withdrawal [32 (6.3%) and 39 (7.8%) patients from the respective arms]. All patients had completed or withdrawn from treatment when the DFS interim analysis was conducted at the previous clinical cut-off (21 January 2021).[13]

The baseline characteristics of the ITT and stage II-IIIA PD-L1 TC ≥1% populations have been previously reported;[13] those of the stage II-IIIA PD-L1 TC ≥50% population are summarised in Table 1. Within this subpopulation, *EGFR* mutations were detected in 14 patients (atezolizumab arm: $n = 6$; BSC arm: $n = 8$), and *ALK* rearrangements were detected in 6 patients (3 in each of the treatment arms).

As of 18 April 2022, the median duration of follow-up was 45.3 months [interquartile range (IQR) 35.5-52.3 months] in the ITT population (median 45.4 months in the atezolizumab arm and 45.2 months in the BSC arm). The median follow-up duration in the stage II-IIIA population was 45.1 months (IQR 34.0-52.10 months): 45.4 months in the atezolizumab arm and 44.8 months in the BSC arm. In the stage II-IIIA PD-L1 TC ≥1% population, the median follow-up duration was 46.0 months (IQR 36.6-53.3 months): 46.9 months in the atezolizumab arm and 44.7 months in the BSC arm.

Overall, 251 deaths (25%) occurred in the ITT population, as required for the first pre-specified OS interim analysis: 127 patients in the atezolizumab arm (25%) and 124 (24.9%) in the BSC arm. Among treated patients, the primary cause of death in the atezolizumab arm was disease relapse [79 (63%)], adverse events [9 (7%)], and other [37 (30%)]. In the BSC arm, the primary cause of death was disease relapse [99 (80%)], followed by adverse events [3 (2%)], and other causes [22 (18%)]. The median OS was not estimable in either arm [stratified HR 0.995 (95% CI 0.78-1.28); Figure 1A]. OS was not formally tested at this interim analysis because formal testing cannot be conducted until a statistically significant difference between arms is observed for DFS in the ITT population.

Pre-specified exploratory OS analyses in the stage II-IIIA and the stage II-IIIA PD-L1 TC ≥1% populations and *post hoc* exploratory OS analyses in other PD-L1 subgroups of the stage II-IIIA population were conducted. In the stage II-IIIA population, death occurred in 115 patients (26.0%) receiving atezolizumab and 116 (26.4%) receiving BSC; the median OS was not estimable [stratified HR 0.95 (95% CI 0.74-1.24); Figure 1B]. In the stage II-IIIA PD-L1 TC ≥1% population, death occurred in 52 (21.0%) and 64 (28.1%) patients in the respective treatment arms; the median OS was not estimable [stratified HR 0.71 (95% CI 0.49-1.03); Figure 1C]. When patients with known *EGFR/ALK* alterations were excluded from this population in a *post hoc* analysis, the unstratified HR was 0.67 (95% CI 0.45-0.98; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.07.001). In the stage II-IIIA PD-L1 TC ≥50% population, which included patients with known *EGFR/ALK* alterations, death occurred in 16 patients (13.9%) receiving atezolizumab and 32 (28.1%) receiving BSC. The median OS was not estimable [unstratified HR 0.43 (95% CI

Table 1. Baseline characteristics in the stage II-IIIA PD-L1 TC ≥50% population

	Atezolizumab ($n = 115$)	Best supportive care ($n = 114$)
Age, median (IQR), years	62 (55-67)	62 (56-67)
Age group		
<65 years	70 (60.9)	68 (59.6)
≥65 years	45 (39.1)	46 (40.4)
Sex		
Male	89 (77.4)	78 (68.4)
Female	26 (22.6)	36 (31.6)
Race		
White	75 (65.2)	86 (75.4)
Asian	36 (31.3)	26 (22.8)
Other	2 (1.7)	0
Unknown	2 (1.7)	2 (1.8)
ECOG performance status		
0	71 (61.7)	60 (52.6)
1	44 (38.3)	53 (46.5)
2	0	1 (0.9)
Tobacco use history		
Never	16 (13.9)	14 (12.3)
Current or previous	99 (86.1)	100 (87.7)
Histology		
Squamous	47 (40.9)	45 (39.5)
Non-squamous	68 (59.1)[a]	69 (60.5)[b]
Stage		
II	62 (53.9)	57 (50.0)
IIIA	53 (46.1)	57 (50.0)
Regional lymph node stage (pN)		
N0	30 (26.1)	21 (18.4)
N1	43 (37.4)	52 (45.6)
N2	42 (36.5)	41 (36.0)
***EGFR* mutation status**[c]		
Detected	6 (5.2)	8 (7.0)
Not detected	60 (52.2)	64 (56.1)
Not tested	49 (42.6)	42 (36.8)
***ALK* rearrangement status**[c]		
Detected	3 (2.6)	3 (2.6)
Not detected	62 (53.9)	62 (54.4)
Not tested	50 (43.5)	49 (43.0)
***EGFR* mutation or ALK rearrangement**[c]		
Detected	9 (7.8)	11 (9.6)
Not detected	52 (45.2)	54 (47.4)
Not tested	54 (47.0)	49 (43.0)
Chemotherapy regimen		
Cisplatin plus docetaxel	13 (11.3)	20 (17.5)
Cisplatin plus gemcitabine	22 (19.1)	17 (14.9)
Cisplatin plus pemetrexed	35 (30.4)	37 (32.5)
Cisplatin plus vinorelbine	45 (39.1)	40 (35.1)
Completed three or four cisplatin cycles[d]	108 (93.9)	100 (87.7)
Type of surgery		
Lobectomy[e]	87 (75.7)	86 (75.4)
Bilobectomy	7 (6.1)	7 (6.1)
Pneumonectomy	20 (17.4)	20 (17.5)
Other	1 (0.9)	1 (0.9)

Data are presented as *n* (%) unless otherwise specified.
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; TC, tumour cell.
[a]Adenocarcinoma in 65 patients (56.5%), large cell in 3 patients (2.6%).
[b]Adenocarcinoma in 64 patients (56.1%), large cell and undifferentiated each in 2 patients (1.8%), and adenosquamous in 1 patient (0.9%).
[c]For patients with non-squamous NSCLC, *EGFR* or *ALK* status was assessed locally or centrally. For the other patients, testing was not required per protocol.
[d]Across chemotherapy doublets.
[e]Includes sleeve lobectomy.

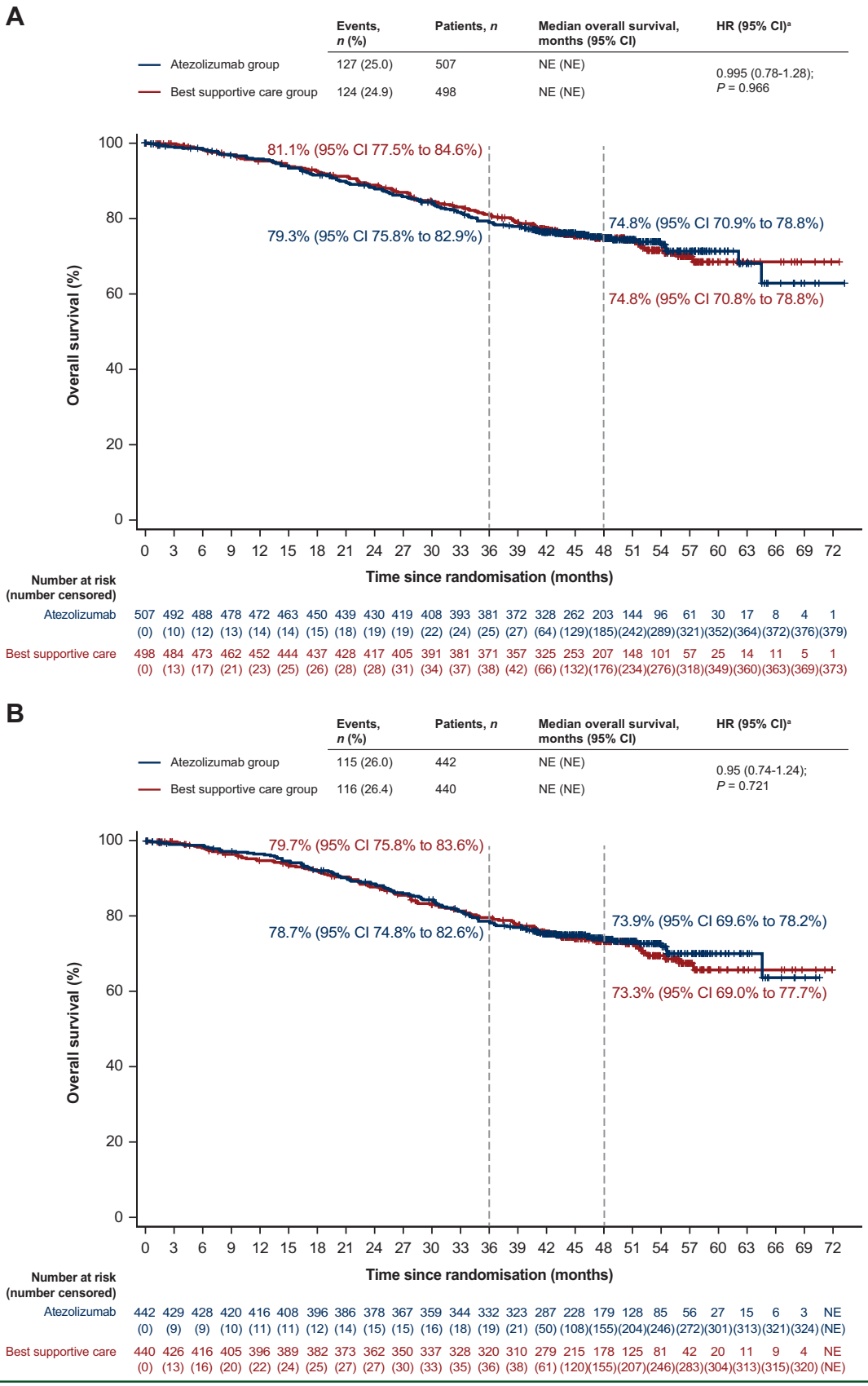

Figure 1. Overall survival. Kaplan–Meier estimates of overall survival in the (A) ITT (randomised stage IB-IIIA), (B) stage II-IIIA, (C) stage II-IIIA PD-L1 TC ≥1%, (D) stage II-IIIA PD-L1 TC ≥50% (including patients with known EGFR/ALK alterations), (E) stage II-IIIA PD-L1 TC ≥50% (excluding patients with known EGFR/ALK alterations), (F) stage II-IIIA PD-L1 TC 1%-49%, and (G) stage II-IIIA PD-L1 TC <1% populations.

CI, confidence interval; ITT, intention-to-treat; NE, not estimable; PD-L1, programmed death-ligand 1; TC, tumour cell.

[a]Stratified.

[b]Unstratified.

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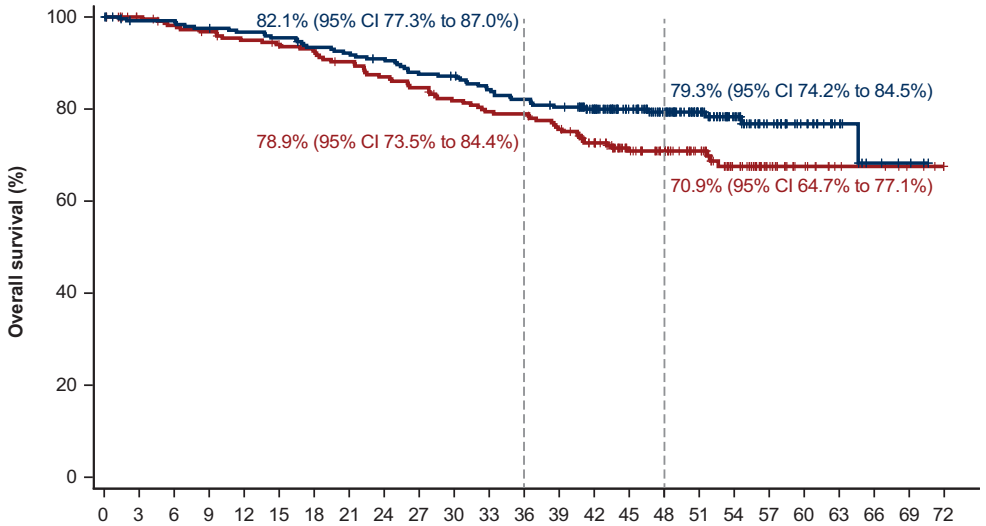
C

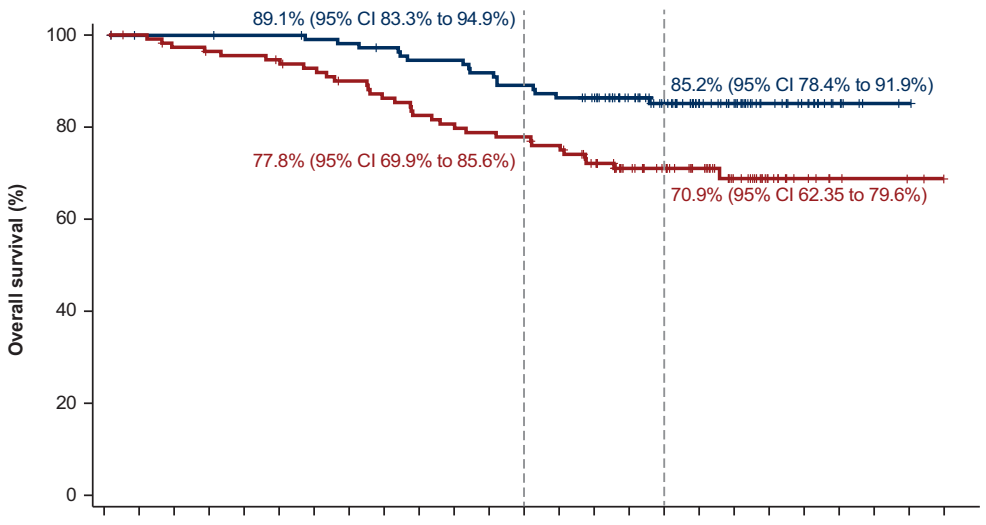
	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[a]
Atezolizumab group	52 (21.0)	248	NE (NE)	0.71 (0.49-1.03); *P* = 0.067
Best supportive care group	64 (28.1)	228	NE (NE)	



Number at risk (number censored)																							
Atezolizumab	248 (0)	241 (5)	241 (5)	237 (5)	234 (6)	231 (6)	225 (7)	222 (7)	218 (8)	210 (8)	208 (9)	200 (10)	195 (10)	190 (11)	172 (28)	140 (60)	116 (83)	83 (116)	56 (142)	37 (160)	23 (174)	12 (185)	5 (191)	3 (193)	NE (NE)
Best supportive care	228 (0)	220 (8)	214 (10)	210 (11)	205 (12)	201 (14)	198 (14)	192 (15)	185 (15)	180 (15)	172 (17)	167 (17)	166 (17)	158 (18)	140 (30)	110 (57)	95 (72)	72 (95)	49 (115)	27 (137)	15 (149)	8 (156)	7 (157)	4 (160)	NE (NE)

D

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	16 (13.9)	115	NE (NE)	0.43 (0.24-0.78); *P* = 0.0045
Best supportive care group	32 (28.1)	114	NE (NE)	

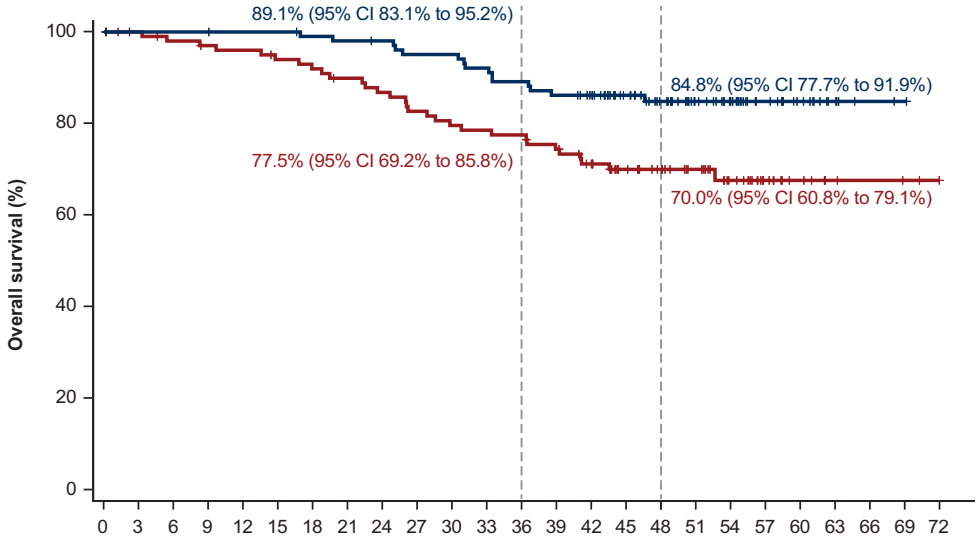


Number at risk (number censored)																							
Atezolizumab	115 (0)	113 (2)	113 (2)	113 (2)	112 (3)	112 (3)	110 (4)	109 (4)	107 (5)	104 (5)	104 (5)	101 (5)	98 (5)	95 (5)	91 (9)	77 (23)	64 (35)	45 (54)	36 (63)	23 (76)	16 (83)	7 (92)	2 (97)	1 (98)	NE (NE)
Best supportive care	114 (0)	112 (2)	108 (3)	106 (4)	105 (4)	101 (6)	99 (6)	96 (7)	92 (7)	88 (7)	85 (7)	84 (7)	83 (7)	79 (8)	71 (13)	57 (26)	49 (34)	39 (44)	26 (56)	14 (68)	8 (74)	4 (78)	3 (79)	2 (80)	NE (NE)

Figure 1. Continued.

E

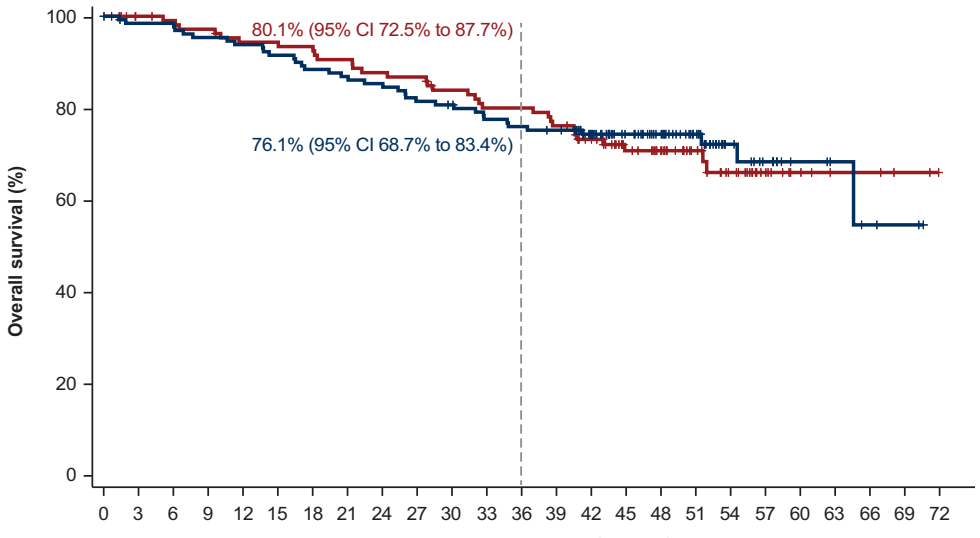
	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	15 (14.2)	106	NE (NE)	0.42 (0.23-0.78); *P* = 0.005
Best supportive care group	30 (29.1)	103	NE (NE)	



Number at risk (number censored)																							
Atezolizumab	106 (0)	104 (2)	104 (2)	104 (2)	103 (3)	103 (3)	101 (4)	100 (4)	99 (5)	96 (5)	96 (5)	93 (5)	90 (5)	87 (5)	83 (9)	69 (23)	58 (33)	41 (50)	32 (59)	20 (71)	13 (78)	6 (85)	2 (89)	1 (90)	NE (NE)
Best supportive care	103 (0)	101 (2)	98 (3)	96 (4)	95 (4)	92 (5)	90 (5)	87 (6)	84 (6)	80 (6)	77 (6)	76 (6)	75 (6)	71 (7)	64 (11)	52 (22)	45 (29)	35 (39)	24 (49)	14 (59)	8 (65)	4 (69)	3 (70)	2 (71)	NE (NE)

F

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	36 (27.1)	133	NE (64.6, NE)	0.95 (0.59-1.54); *P* = 0.845
Best supportive care group	32 (28.1)	114	NE (NE)	



Number at risk (number censored)																							
Atezolizumab	133 (0)	128 (3)	128 (3)	124 (3)	122 (3)	119 (3)	115 (3)	113 (3)	111 (3)	106 (3)	104 (4)	99 (5)	97 (5)	95 (6)	81 (19)	63 (37)	52 (48)	38 (62)	20 (79)	14 (84)	7 (91)	5 (93)	3 (94)	2 (95)	NE (NE)
Best supportive care	114 (0)	108 (6)	106 (7)	104 (7)	100 (8)	100 (8)	99 (8)	96 (8)	93 (8)	92 (8)	87 (10)	83 (10)	83 (10)	79 (10)	69 (17)	53 (31)	46 (38)	33 (51)	23 (59)	13 (69)	7 (75)	4 (78)	4 (78)	2 (80)	NE (NE)

Figure 1. Continued.

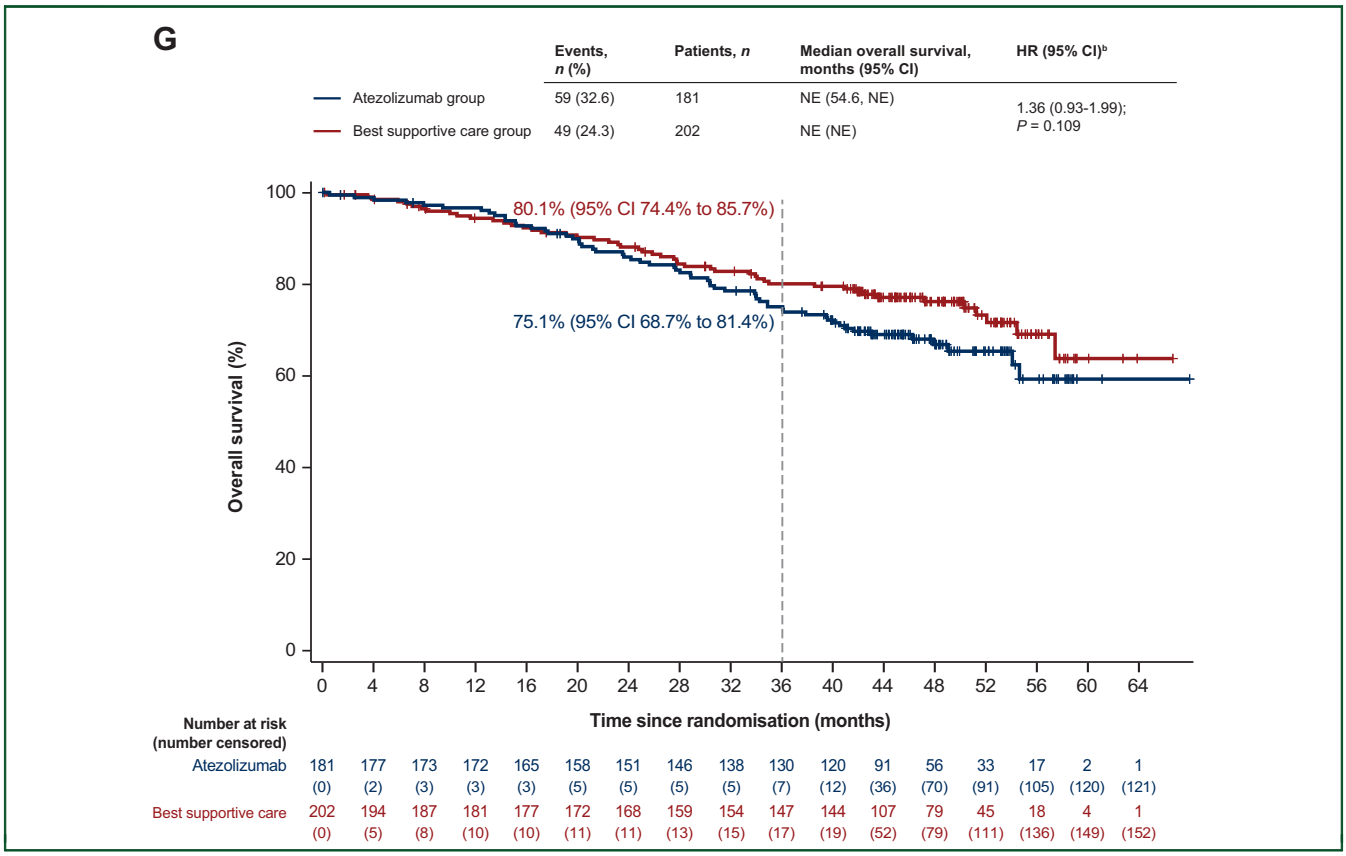


Figure 1. Continued.

0.24-0.78); Figure 1D]. In some countries in which atezolizumab has been approved following chemotherapy as treatment for resected stage II-IIIA PD-L1 TC ≥50% NSCLC, the indication excludes patients with *EGFR/ALK* alterations. When the 20 patients with known *EGFR/ALK* alterations from this population were excluded, the number of deaths was 15 (14.2%) and 30 (29.1%) patients in the respective treatment arms [unstratified HR 0.42 (95% CI 0.23-0.78); Figure 1E]. In the stage II-IIIA PD-L1 TC 1%-49% population, death occurred in 36 (27.1%) and 32 (28.1%) patients in the respective treatment arms; the median OS was not estimable [unstratified HR 0.95 (95% CI 0.59-1.54); Figure 1F]. In the stage II-IIIA PD-L1 TC <1% population, death occurred in 59 patients (32.6%) in the atezolizumab arm and 49 patients (24.3%) in the BSC arm [unstratified HR 1.36 (95% CI 0.93-1.99); Figure 1G].

Pre-specified exploratory OS analyses at landmark timepoints were conducted in the ITT, stage II-IIIA, and stage II-IIIA PD-L1 TC ≥1% populations; *post hoc* analyses were conducted in the PD-L1 TC ≥50%, TC 1%-49%, and TC <1% subgroups of the stage II-IIIA population. The 3-year OS rates in the ITT population were 79.3% in the atezolizumab arm and 81.1% in the BSC arm (Figure 1A). In the stage II-IIIA population, 3-year OS rates in the respective treatment arms were 78.7% and 79.7% overall, 82.1% and 78.9% in stage II-IIIA patients with PD-L1 TC ≥1%, 76.1% and 80.1% in stage II-IIIA patients with PD-L1 TC 1%-49%, 89.1% and 77.8% in stage II-IIIA patients with PD-L1 TC ≥50%, and 75.1% and 80.1% in stage II-IIIA patients with PD-L1 TC <1% (Figure 1B-G).

OS subgroup analyses showed HRs generally favouring atezolizumab versus BSC across most subgroups in the stage II-IIIA PD-L1 TC ≥1% and PD-L1 TC ≥50% populations (Figure 2). Exploratory subgroup analyses of patients in the stage II-IIIA PD-L1 TC 1%-49% and PD-L1 TC <1% populations showed that OS was generally similar among patient subgroups in each population (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.07.001).

In the ITT population, 122 patients (24.1%) in the atezolizumab arm and 145 patients (29.1%) in the BSC arm received subsequent non-protocol anticancer therapy (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.07.001).

The safety-assessable population included 495 patients in each treatment arm. The median duration of atezolizumab treatment was 10.4 months (IQR 4.8-10.6 months), with a median of 16 cycles (IQR 7-16 cycles) received by the DFS analysis cut-off on 21 January 2021,[13] by which time all patients had completed or withdrawn from treatment.

At the clinical cut-off on 18 April 2022, adverse events of any grade had been reported in 458 (92.5%) of 495 patients receiving atezolizumab and 351 (70.9%) of 495 patients receiving BSC (Table 2, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.07.001). Grade 3 or 4 adverse events occurred in 109 (22.0%) and 57 (11.5%)

A

Stage II-IIIA PD-L1 TC ≥1%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	476	248	NE (NE)	228	NE (NE)	0.71 (0.49-1.03)
Age						
<65 years	287	156	NE (64.6-NE)	131	NE (NE)	0.65 (0.40-1.07)
≥65 years	189	92	NE (NE)	97	NE (NE)	0.78 (0.45-1.35)
Sex						
Male	318	171	NE (NE)	147	NE (NE)	0.67 (0.43-1.04)
Female	158	77	NE (64.6-NE)	81	NE (NE)	0.73 (0.38-1.40)
Race						
White	328	162	NE (64.6-NE)	166	NE (NE)	0.72 (0.48-1.09)
Asian	134	78	NE (NE)	56	NE (NE)	0.66 (0.27-1.58)
ECOG PS						
0	265	140	NE (NE)	125	NE (NE)	0.51 (0.30-0.87)
1	209	107	64.6 (NE)	102	NE (NE)	0.96 (0.58-1.59)
Tobacco use history						
Never	91	51	NE (NE)	40	NE (51.6-NE)	0.69 (0.29-1.61)
Previous	310	163	NE (NE)	147	NE (NE)	0.64 (0.40-1.02)
Current	75	34	64.6 (64.6-NE)	41	NE (52.6-NE)	1.01 (0.45-2.25)
Histology						
Squamous	181	96	64.6 (NE)	85	NE (NE)	0.85 (0.48-1.50)
Non-squamous	295	152	NE (NE)	143	NE (NE)	0.61 (0.38-0.99)
Stage						
II	244	131	NE (64.6-NE)	113	NE (NE)	0.71 (0.40-1.26)
IIIA	232	117	NE (NE)	115	NE (NE)	0.71 (0.44-1.15)
Regional lymph node stage (pN)						
N0	106	60	NE (NE)	46	NE (NE)	0.70 (0.28-1.72)
N1	194	100	NE (64.6-NE)	94	NE (NE)	0.57 (0.30-1.08)
N2	176	88	NE (NE)	88	NE (51.6-NE)	0.84 (0.50-1.40)
Type of surgery						
Lobectomy	358	185	NE (NE)	173	NE (NE)	0.63 (0.40-0.99)
Bilobectomy	24	15	NE (NE)	9	NE (26.2-NE)	0.29 (0.05-1.74)
Pneumonectomy	85	43	NE (38.5-NE)	42	NE (36.4-NE)	1.02 (0.52-1.97)
Chemotherapy regimen						
Cisplatin + docetaxel	71	34	NE (NE)	37	40.8 (26.2-NE)	0.47 (0.21-1.04)
Cisplatin + gemcitabine	75	47	64.6 (54.6-NE)	28	NE (43.5-NE)	1.08 (0.43-2.70)
Cisplatin + pemetrexed	169	84	NE (NE)	85	NE (NE)	0.88 (0.45-1.72)
Cisplatin + vinorelbine	161	83	NE (NE)	78	NE (NE)	0.55 (0.28-1.10)
***EGFR* mutation status**						
Yes	43	23	NE (NE)	20	NE (51.6-NE)	0.77 (0.22-2.67)
No	248	123	NE (NE)	125	NE (NE)	0.71 (0.42-1.21)
Not tested	185	102	64.6 (NE)	83	NE (NE)	0.65 (0.37-1.13)
***ALK* rearrangement status**						
Yes	23	12	NE (NE)	11	NE (NE)	1.87 (0.17-20.65)
No	254	133	NE (NE)	121	NE (NE)	0.66 (0.40-1.09)
Not tested	199	103	64.6 (NE)	96	NE (NE)	0.71 (0.41-1.24)
***EGFR* mutation or *ALK* rearrangement status**						
Yes	66	35	NE (NE)	31	NE (NE)	0.97 (0.33-2.89)
No	203	103	NE (NE)	100	NE (NE)	0.58 (0.33-1.03)
Not tested	207	110	64.6 (NE)	97	NE (NE)	0.76 (0.44-1.30)

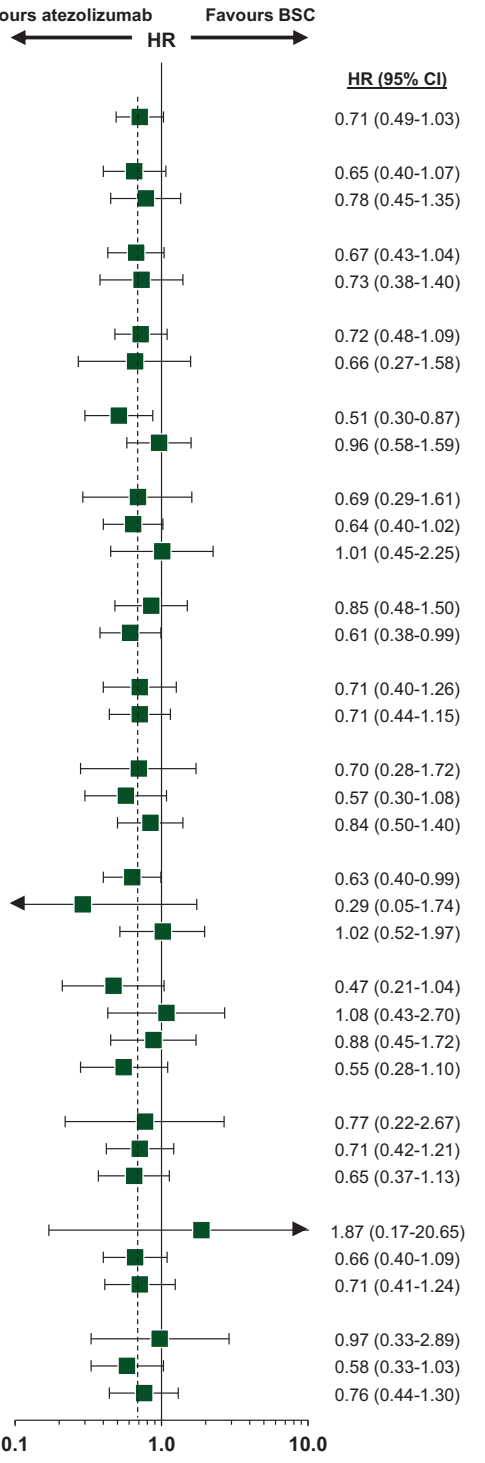


Figure 2. Subgroup analysis of OS. Forest plots of OS in key subgroups of the stage II-IIIA NSCLC population with (A) PD-L1 TC ≥1% and (B) PD-L1 TC ≥50%. OS HRs are unstratified except for the OS HR in all patients.

BSC, best supportive care; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not estimable; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1.

patients in the respective arms, and grade 5 adverse events occurred in 9 (1.8%) and 3 (0.6%) patients in the respective arms. The incidence of grade 3 or 4 treatment-related adverse events was unchanged since the previous cut-off, having occurred in 53 patients (10.7%) receiving atezolizumab.[13] The incidence of treatment-related grade 5 adverse events in 4 (0.8%) patients receiving atezolizumab was also unchanged (these were myocarditis, interstitial lung disease, multiple organ dysfunction syndrome, and acute myeloid leukaemia).[13] No new adverse events with fatal outcomes

B

Stage II-IIIA PD-L1 TC ≥50%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	229	115	NE (NE)	114	NE (NE)	0.43 (0.24-0.78)
Age						
<65 years	138	70	NE (NE)	68	NE (NE)	0.44 (0.20-0.97)
≥65 years	91	45	NE (NE)	46	NE (52.6-NE)	0.42 (0.17-1.04)
Sex						
Male	167	89	NE (NE)	78	NE (NE)	0.39 (0.19-0.80)
Female	62	26	NE (NE)	36	NE (NE)	0.58 (0.20-1.68)
Race						
White	161	75	NE (NE)	86	NE (NE)	0.41 (0.20-0.84)
Asian	62	36	NE (NE)	26	NE (NE)	0.39 (0.09-1.63)
ECOG PS						
0	131	71	NE (NE)	60	NE (NE)	0.38 (0.16-0.90)
1	97	44	NE (NE)	53	NE (NE)	0.51 (0.22-1.19)
Tobacco use history						
Never	30	16	NE (NE)	14	NE (41.1-NE)	0.58 (0.13-2.62)
Previous	161	83	NE (NE)	78	NE (NE)	0.35 (0.16-0.76)
Current	38	16	NE (NE)	22	NE (38.9-NE)	0.74 (0.22-2.53)
Histology						
Squamous	92	47	NE (NE)	45	NE (NE)	0.58 (0.22-1.51)
Non-squamous	137	68	NE (NE)	69	NE (NE)	0.36 (0.17-0.79)
Stage						
II	119	62	NE (NE)	57	NE (NE)	0.63 (0.28-1.44)
IIIA	110	53	NE (NE)	57	NE (NE)	0.30 (0.12-0.74)
Regional lymph node stage (pN)						
N0	51	30	NE (NE)	21	NE (NE)	0.74 (0.21-2.55)
N1	95	43	NE (NE)	52	NE (NE)	0.38 (0.14-1.07)
N2	83	42	NE (NE)	41	NE (41.1-NE)	0.36 (0.14-0.95)
Type of surgery						
Lobectomy	169	84	NE (NE)	85	NE (NE)	0.32 (0.15-0.69)
Bilobectomy	14	7	NE (NE)	7	NE (NE)	0.78 (0.05-12.55)
Pneumonectomy	40	20	NE (38.5-NE)	20	NE (28.6-NE)	0.76 (0.25-2.25)
Chemotherapy regimen						
Cisplatin + docetaxel	33	13	NE (NE)	20	NE (26.2-NE)	0.18 (0.02-1.47)
Cisplatin + gemcitabine	39	22	NE (NE)	17	NE (43.5-NE)	0.64 (0.16-2.54)
Cisplatin + pemetrexed	72	35	NE (NE)	37	NE (NE)	0.49 (0.17-1.42)
Cisplatin + vinorelbine	85	45	NE (NE)	40	NE (NE)	0.44 (0.16-1.19)
***EGFR* mutation status**						
Yes	14	6	NE (NE)	8	NE (22.3-NE)	0.65 (0.06-7.15)
No	124	60	NE (NE)	64	NE (NE)	0.35 (0.15-0.83)
Not tested	91	49	NE (NE)	42	NE (NE)	0.51 (0.21-1.27)
***ALK* rearrangement status**						
Yes	6	3	NE (NE)	3	NE (NE)	NE (NE)
No	124	62	NE (NE)	62	NE (NE)	0.41 (0.19-0.90)
Not tested	99	50	NE (NE)	49	NE (NE)	0.48 (0.19-1.23)
***EGFR* mutation or *ALK* rearrangement status**						
Yes	20	9	NE (NE)	11	NE (NE)	0.56 (0.05-6.14)
No	106	52	NE (NE)	54	NE (NE)	0.37 (0.15-0.89)
Not tested	103	54	NE (NE)	49	NE (NE)	0.51 (0.21-1.24)

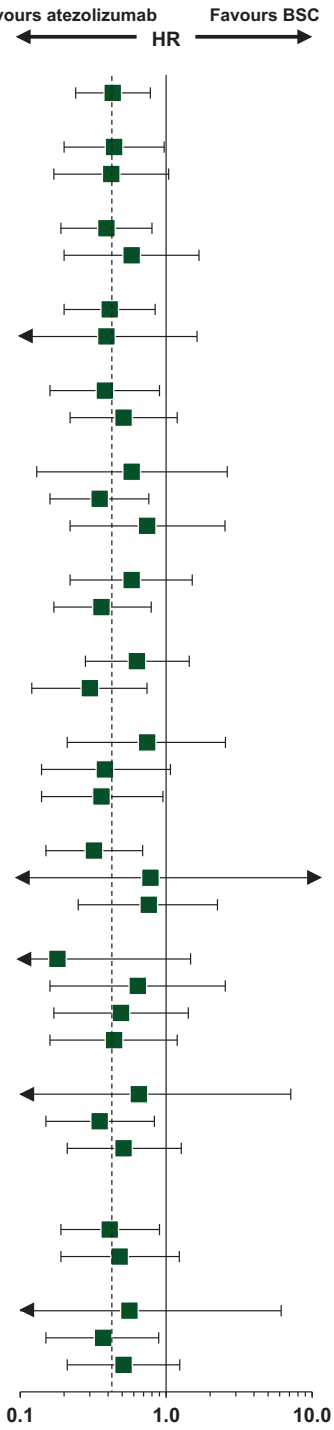


Figure 2. **Continued.**

occurred since the previous clinical cut-off; however, a previously reported death was updated to a fatal adverse event (death due to unknown cause that occurred 13 days after the last atezolizumab dose at cycle 16, which was deemed unrelated to atezolizumab by the investigator). Adverse events leading to atezolizumab withdrawal occurred in 90 (18.2%) patients in the atezolizumab arm.

Serious adverse events occurred in 88 (17.8%) patients receiving atezolizumab and 42 (8.5%) patients receiving BSC. Treatment-related serious adverse events and adverse events leading to atezolizumab treatment interruption or withdrawal were reported at the previous cut-off.[13] In the atezolizumab arm, the most common treatment-related serious adverse events were pneumonitis in 4 (0.8%)

Table 2. Safety summary in the safety-assessable population

	Atezolizumab (n = 495)	Best supportive care (n = 495)
Any-grade adverse event	458 (92.5)[a]	351 (70.9)
Treatment-related adverse event	336 (67.9)	0
Grade 3/4 adverse event	109 (22.0)	57 (11.5)
Treatment-related grade 3/4 adverse event	53 (10.7)	0
Serious adverse event	88 (17.8)	42 (8.5)
Treatment-related serious adverse event	37 (7.5)	0
Grade 5 adverse event	9 (1.8)[a]	3 (0.6)
Treatment-related grade 5 adverse event	4 (0.8)	0
Adverse event leading to atezolizumab dose interruption	142 (28.7)	0
Adverse event leading to atezolizumab withdrawal	90 (18.2)	0
Any-grade AESI	258 (52.1)	47 (9.5)
Grade 3/4 AESI	39 (7.9)	3 (0.6)
Treatment-related grade 3/4 AESI	31 (6.3)	0
Grade 5 AESI	2 (0.4)	0
Treatment-related grade 5 AESI	2 (0.4)	0
Any-grade AESI leading to dose interruption of atezolizumab	58 (11.7)	0
Any-grade AESI leading to atezolizumab discontinuation	52 (10.5)	0

Data are presented as n (%).
AESI, adverse event of special interest.
[a]A death previously recorded as 'other' was updated to a grade 5 adverse event of unknown cause, deemed unrelated to atezolizumab by the investigator.

patients and interstitial lung disease and pyrexia each in 3 (0.6%) patients.

AESIs, also known as immune-mediated adverse events, occurred in 258 (52.1%) patients receiving atezolizumab and 47 (9.5%) patients receiving BSC. Grade 3 or 4 AESIs were reported in 39 (7.9%) and 3 (0.6%) patients in the respective arms. Grade 5 AESIs (immune-mediated pneumonitis and immune-mediated myocarditis) occurred in 2 (0.4%) patients receiving atezolizumab, as reported previously.[13] AESIs of any grade that required the use of corticosteroids occurred in 61 (12.3%) and 4 (0.8%) patients in the respective arms. All new AESIs reported since the previous cut-off (in a total of two additional patients in the atezolizumab arm) were grade 1 or 2: hyperthyroidism, hepatic laboratory abnormality, and infusion-related reaction each occurred in one of these patients (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.07.001). The most frequently reported AESIs for atezolizumab (by medical concept or group of related MedDRA preferred terms) were rash [91 (18.4%) patients in the atezolizumab arm and 11 (2.2%) patients in the BSC arm], hepatitis [diagnosis and laboratory abnormalities; 87 (17.6%) and 22 (4.4%) patients in the respective arms], hypothyroidism [84 (17.0%) and 3 (0.6%) patients in the respective arms], and hyperthyroidism [33 (6.7%) and 4 (0.8%) patients in the respective arms]. No new AESI medical concept categories were observed since the previous clinical cut-off. Since the 21 January 2021 cut-off, of the ongoing AESIs at that time, two cases of immune-mediated rash, one case of immune-mediated hypothyroidism, and two cases of immune-mediated diabetes resolved, as did all cases of immune-mediated hepatitis (diagnosis). Overall, the majority of the AESIs had resolved by the 18 April 2022 cut-off.

DISCUSSION

While OS could not yet be formally tested in the ITT population, these exploratory analyses, with deaths in 25% of patients, showed OS improvement in favour of atezolizumab versus BSC in the stage II-IIIA PD-L1 TC $\geq$1% population [stratified HR 0.71 (95% CI 0.49-1.03)]. The OS benefit with atezolizumab versus BSC was strongest in the stage II-IIIA PD-L1 TC $\geq$50% population [unstratified HR 0.43 (95% CI 0.24-0.78)]. When the patients with known *EGFR* or *ALK* alterations were excluded from the stage II-IIIA PD-L1 TC $\geq$50% subpopulation, the OS results remained consistent. No OS improvement in favour of atezolizumab was seen versus BSC in the ITT or stage II-IIIA populations, and no OS benefit was seen with atezolizumab in the stage II-IIIA PD-L1 TC $<$1% population. However, due to the exploratory nature of the subgroup analyses and lack of formal testing, these data should be interpreted with caution. After an additional 13 months of follow-up, the safety profile remained largely unchanged since the previous cut-off, with no new or unexpected safety signals observed and no new AESI medical concept categories emerging.

The OS data at this interim analysis (18 April 2022, cut-off) appear to be generally reflective of the DFS data from the DFS interim analysis (21 January 2021, cut-off) (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.07.001).[13,15] The 3-year OS rates and HRs at the most recent clinical cut-off showed greater improvements with atezolizumab versus BSC in the PD-L1-positive than in the overall stage II-IIIA population and even more substantial improvements in the stage II-IIIA PD-L1-high (i.e. PD-L1 TC $\geq$50%) population. Although no survival benefit was seen with atezolizumab in the stage II-IIIA PD-L1-low (TC 1%-49%) subgroup at this OS interim analysis, a numerically improved DFS with atezolizumab versus BSC was observed in this subgroup [HR for disease recurrence or death was 0.87 (95% CI 0.60-1.26)].[13] In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease could significantly reduce cost and resource utilisation and thereby benefit patients and payers.[16-20]

Several other phase III clinical trials of adjuvant programmed death-1/PD-L1 inhibitors in resectable stage IB-IIIA NSCLC are in progress, including PEARLS/KEYNOTE-091 (pembrolizumab versus placebo),[21] BR.31 (durvalumab versus placebo),[22] ANVIL (nivolumab), and ALCHEMIST (pembrolizumab plus platinum doublet chemotherapy versus pembrolizumab following chemotherapy versus observation following chemotherapy).[2,23,24] Unlike in IMpower010, adjuvant chemotherapy before immunotherapy is permitted but not mandatory in the first three studies. The PEARLS/KEYNOTE-091 study evaluated the co-primary endpoints DFS and OS in the overall stage IB-IIIA population and in patients with a PD-L1 tumour proportion score of $\geq$50%.[21] At the second interim analysis, DFS

was significantly improved with pembrolizumab versus BSC in the overall population (HR 0.76; $P = 0.0014$), but in contrast to IMpower010, the significance boundary was not crossed in the PD-L1-high population (HR 0.82; 95% CI 0.57-1.18; $P = 0.14$).[21] With 18% of the patients having died, the significance boundary for OS was not crossed in the overall population (HR for death was 0.87; $P = 0.17$). Approximately 14% of patients did not receive chemotherapy in KEYNOTE-091 and appear to have derived no benefit from pembrolizumab,[21] which may suggest that chemotherapy in this setting could play a role in contributing to survival benefit. The primary endpoint of BR.31 is DFS in the overall study population and in PD-L1-positive patients (TC $\geq$25% and $\geq$1%).[25] The co-primary endpoints of ANVIL are OS and DFS.[24] The primary endpoint of ALCHEMIST is DFS, with OS and DFS by PD-L1 status as secondary endpoints; at the time of writing, this study was still recruiting patients.[23]

In IMpower010, all patients had completed study treatment and observation by the DFS interim analysis, and minimal changes to the AESI data were seen since then. The results of this updated safety analysis were consistent with those at the DFS interim analysis,[13] and no new safety signals emerged. The majority of AESIs were low grade and manageable by treatment interruption or with the use of hormone replacement therapy or systemic corticosteroids. Most AESIs had resolved by this clinical cut-off.

Study strengths include the large global study population and the standardised chemotherapy regimens.[11] Study limitations include the open-label design.[13] A limitation of this analysis was that, because only 20 patients in the PD-L1 TC $\geq$50% subpopulation had known *EGFR* or *ALK* alterations, it was not meaningful to compare the OS outcomes directly between patients with PD-L1-high NSCLC with and without these alterations. More than 40% of patients with PD-L1 TC $\geq$50% disease were not tested for these biomarkers at baseline. Testing for these alterations was not required in IMpower010 because it was not standard practice to determine *EGFR* or *ALK* status in non-metastatic NSCLC until adjuvant osimertinib was approved for *EGFR*-mutated NSCLC based on ADAURA.[6] Additionally, 40% of these patients had squamous NSCLC, for which *EGFR* or *ALK* testing was not required. Hence, local results needed only to be provided if they were available. Central testing for *EGFR* and *ALK* alterations was conducted for patients with non-squamous histology if tissue was available. Patient subgroups within the PD-L1 $\geq$1% and PD-L1 $\geq$50% populations were small; hence the findings of these exploratory subgroup analyses should be interpreted with caution.

In conclusion, although OS data remain immature for the ITT population and IMpower010 was not powered to show differences in treatment effects in patient subgroups, these exploratory OS data indicate a positive trend in favour of atezolizumab versus BSC in patients with resected stage II-IIIA PD-L1 TC $\geq$1% NSCLC, primarily driven by the PD-L1 TC $\geq$50% subgroup. No new safety signals were identified with 13 months' additional follow-up. IMpower010 will continue until the final DFS analysis, with further OS follow-up and analyses in the ITT and other subpopulations planned.

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DISCLOSURE

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DATA SHARING

For eligible studies, qualified researchers can request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_ we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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