ORIGINAL ARTICLE

Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial

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Received 12 March 2020; accepted 23 March 2020
Available online - 14 April 2020

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Disclosure: Dr. Jotte received a grant and nonfinancial support from F. Hoffmann-La Roche, during the conduct of the study, and editorial support funded by the sponsor and provided by an independent medical writer under the guidance of the authors. Cappuzzo has been a consultant/advisor for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche, and Takeda; received a grant and nonfinancial support from F. Hoffmann-La Roche during the conduct of the study; and received editorial support funded by the sponsor and provided by an independent medical writer under the guidance of the authors. Rodríguez-Abreu has participated in speakers' bureaus for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche; received a grant and nonfinancial support from F. Hoffmann-La Roche during the conduct of the study; and received editorial support funded by the sponsor and provided by an independent medical writer under the guidance of the authors. Hussein has participated in speakers' bureaus for Bristol-Myers Squibb, Incyte, and Pfizer. Soo has received grants from AstraZeneca and Boehringer-Ingelheim and personal fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Takeda, and Yuhan. Conter has received personal fees from F. Hoffmann-La Roche Canada. Kozuki has received grants from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical Company, Eli Lilly Japan, Merck Biopharma, and Taiho and personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical Company, Eli Lilly Japan, Kyowa Hakko Kirin, Merck Sharp & Dohme, Nippon Boehringer-Ingelheim, Nippon Kayaku, Novartis, Ono, Pfizer Japan, and Taiho. Socinski has participated in speakers' bureaus for Genentech; has received honoraria and research funding from Genentech; received a grant from Genentech/Roche; and received editorial support funded by the sponsor. Huang, Graupner, Sun, Hoang, Jessop, McCleland, Ballinger, and Sandler are employees of Genentech/Roche. Huang, Ballinger, and Sandler have stock/other ownership in Roche. Sandler has issued a patent on the basis of IMpower150. Jessop, Sun, Huang, Ballinger, Sandler, and Graupner have stock/other ownership in Roche. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2020.03.028

ABSTRACT

Introduction: Cytotoxic agents have immunomodulatory effects, providing a rationale for combining atezolizumab (anti-programmed death-ligand 1 [anti–PD-L1]) with chemotherapy. The randomized phase III IMpower131 study (NCT02367794) evaluated atezolizumab with platinum-based chemotherapy in stage IV squamous NSCLC.

Methods: A total of 1021 patients were randomized 1:1:1 to receive atezolizumab+carboplatin+paclitaxel (A+CP) (n = 338), atezolizumab+carboplatin+nab-paclitaxel (A+CnP) (n = 343), or carboplatin+nab-paclitaxel (CnP) (n = 340) for four or six 21-day cycles; patients randomized to the A+CP or A+CnP arms received atezolizumab maintenance therapy until progressive disease or loss of clinical benefit. The coprimary end points were investigator-assessed progression-free survival (PFS) and overall survival (OS) in the intention-to-treat (ITT) population. The secondary end points included PFS and OS in PD-L1 subgroups and safety. The primary PFS (January 22, 2018) and final OS (October 3, 2018) for A+CnP versus CnP are reported.

Results: PFS improvement with A+CnP versus CnP was seen in the ITT population (median, 6.3 versus 5.6 mo; hazard ratio [HR] = 0.71, 95% confidence interval [CI]: 0.60–0.85; $p = 0.0001$). Median OS in the ITT population was 14.2 and 13.5 months in the A+CnP and CnP arms (HR = 0.88, 95% CI: 0.73–1.05; $p = 0.16$), not reaching statistical significance. OS improvement with A+CnP versus CnP was observed in the PD-L1–high subgroup (HR = 0.48, 95% CI: 0.29–0.81), despite not being formally tested. Treatment-related grade 3 and 4 adverse events and serious adverse events occurred in 68.0% and 47.9% (A+CnP) and 57.5% and 28.7% (CnP) of patients, respectively.

Conclusions: Adding atezolizumab to platinum-based chemotherapy significantly improved PFS in patients with first-line squamous NSCLC; OS was similar between the arms.

Keywords: Squamous NSCLC; Atezolizumab; Nab-paclitaxel; Carboplatin; IMpower131

Introduction

Platinum-based chemotherapy remains a first-line treatment option for many patients with advanced squamous NSCLC, which accounts for 25% to 30% of lung cancers.[1-3] Nevertheless, these treatment options provide limited efficacy, with a median overall survival (OS) of less than 1 year.[3] More recently, the introduction of pembrolizumab to platinum-based chemotherapy for the first-line treatment of patients with metastatic squamous NSCLC has led to significant improvement in OS, with a median of 15.9 months.[4] In patients with programmed death-ligand 1 (PD-L1) expression on greater than or equal to 1% of tumor cells (TCs), pembrolizumab monotherapy has resulted in significant OS improvement compared to that observed with platinum-based chemotherapy,[5] representing a chemotherapy-free treatment option.

A significant OS benefit with atezolizumab (anti–PD-L1 antibody) versus docetaxel was reported in patients with previously treated NSCLC, regardless of PD-L1 expression or tumor histology.[6] On the basis of these and other data, atezolizumab monotherapy was approved for patients with metastatic NSCLC that progressed during or after platinum-based chemotherapy.[7,8] In the first-line setting, atezolizumab monotherapy has resulted in significant OS improvement compared to that observed with platinum-based chemotherapy in patients with high PD-L1 levels (≥50% TCs or ≥10% tumor-infiltrating immune cells [ICs]) independent of tumor histology.[9]

Cytotoxic agents can exhibit positive immunomodulatory effects by releasing high levels of tumor antigens and reinstating immunosurveillance, suggesting that chemotherapy may enhance atezolizumab's antitumor activity.[10] The phase III IMpower130 study reported that the addition of atezolizumab to carboplatin and nab-paclitaxel for the first-line treatment of patients with metastatic nonsquamous NSCLC provided a clinically meaningful and statistically significant benefit in OS and progression-free survival (PFS) versus chemotherapy alone; thus, this atezolizumab regimen received approval in the United States and the European Union.[11-13] Furthermore, in the IMpower150 study, the addition of atezolizumab to bevacizumab, carboplatin, and paclitaxel for the first-line treatment of patients with metastatic nonsquamous NSCLC provided significant improvements in PFS and OS, resulting in the approval of the regimen in this patient population.[14,15] Here, the efficacy and safety from the phase III IMpower131 study (NCT02367794), which evaluated the combination of atezolizumab and carboplatin-taxane doublet chemotherapy as first-line therapy in patients with stage IV squamous NSCLC, are reported.

Materials and Methods

Study Design and Treatment

In the global, open-label, phase III IMpower131 study, the patients were randomized 1:1:1 to receive atezolizumab+carboplatin+paclitaxel (A+CP), atezolizumab+carboplatin+nab-paclitaxel (A+CnP), or

carboplatin+nab-paclitaxel (CnP). Stratification factors were sex (male or female), presence of liver metastases (yes or no), and PD-L1 expression by immunohistochemistry (TC3 and any IC versus TC0/1/2 and IC2/3 versus TC0/1/2 and IC0/1). The patients received four or six 21-day cycles of induction treatment (number of cycles per investigator discretion, chosen before therapy initiation). Atezolizumab was administered at 1200 mg intravenously (IV; day 1), carboplatin at an area under the concentration−time curve of 6 mg/mL/min IV (day 1), paclitaxel at 200 mg/m^2 IV (175 mg/m^2 for Asian race/ethnicity; day 1), and nab-paclitaxel at 100 mg/m^2 IV (days 1, 8, and 15). After induction, patients in the A+CP and A+CnP arms continued atezolizumab until disease progression per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or loss of clinical benefit. Crossover to atezolizumab was not allowed.

Patient Criteria

Eligible patients had histologically or cytologically confirmed stage IV squamous NSCLC per the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM Staging system,[16] had not received chemotherapy for stage IV squamous NSCLC, had measurable disease per the RECIST version 1.1, had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had tumor tissue available for central PD-L1 testing. Patients known to have *EGFR* mutations or *ALK* fusion oncogene were eligible for the study but had to have experienced disease progression on or intolerance to one or more approved tyrosine kinases or ALK inhibitors, respectively; testing for *EGFR* and *ALK* status was not mandated. Exclusion criteria included active or untreated central nervous system metastases; history of autoimmune disease; previous immune checkpoint blockade therapies with the exception of anti–CTLA-4 therapy, provided the last dose was given more than or equal to 6 weeks before randomization; and systemic immunosuppressive medications less than 2 weeks before randomization.

End Points and Assessments

The coprimary end points were investigator-assessed PFS per the RECIST version 1.1 and OS in the intention-to-treat (ITT) population. The secondary end points included investigator-assessed objective response rate (ORR), duration of response (DOR), PFS, and OS evaluated in PD-L1 subgroups (defined as TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3) and in the T-effector (Teff) population. Additional PD-L1 subpopulations were explored: TC3 or IC3 (high expression), TC1/2 or IC1/2 (low expression), and TC0 and IC0 (negative). Baseline PD-L1 tumor expression was evaluated in archival tissue or tissue obtained from a biopsy at screening using the SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ) and was scored by a central laboratory, as previously described[6] (Supplementary Table 1). The Teff gene signature was defined by the average expression of *CD274*, *CXCL9*, and *IFN*γ in RNA isolated from tumor tissue and was measured using quantitative real-time polymerase chain reaction relative to the expression of a control gene (Roche Molecular Systems, Pleasanton, CA). The Teff population was defined as patients in the ITT population with a Teff signature score greater than or equal to −1.91.

The safety and tolerability of the study treatment were evaluated, and adverse events (AEs) were assessed per the National Cancer Institute Common Terminology Criteria for AEs version 4.0. Tumor assessments were performed at baseline, every 6 weeks for the first 48 weeks after cycle 1, day 1, and every 9 weeks thereafter until disease progression per the RECIST version 1.1 or loss of clinical benefit for patients who continued atezolizumab after initial disease progression.

Statistical Analysis

The coprimary end points of PFS and OS in the ITT population were tested first between the A+CnP and CnP arms (Supplementary Fig. 2). To control the type I error rate at 0.05 (two-sided), the alpha was split and a two-sided alpha of 0.006 and 0.044 was allocated to PFS and OS, respectively. If PFS was statistically significant, the alpha would be recycled, and OS would be tested at a two-sided significance level of 0.05. Only if OS between the A+CnP and CnP arms was statistically significant would PFS and OS be tested with alpha allocation between the A+CP and CnP arms (Supplementary Fig. 8). At the time of the primary PFS analysis, the first planned interim analysis of OS was performed. For the first interim analysis of OS, a nominal alpha (0.0001) was spent.

Stratified log-rank tests were used for treatment comparisons of PFS and OS, using the same stratification factors as those for randomization (sex, baseline liver metastases, and PD-L1 status). Kaplan-Meier methodology was used to estimate median PFS and median OS for each treatment arm. Brookmeyer-Crowley methodology was used to calculate 95% confidence intervals (CIs) for the medians. A stratified Cox regression model was used to estimate hazard ratios (HRs). Analyses of prespecified subgroups were performed using unstratified HRs estimated from Cox proportional hazard models and Kaplan-Meier estimates.

Study Oversight

F. Hoffmann-La Roche Ltd./Genentech, Inc., sponsored the study, provided the study drugs, and collaborated with the academic authors on the study design, data collection, analysis, and interpretation. This study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Independent ethics committees for each site approved the protocol, all authors verified that the study was conducted per protocol, and all included patients gave written informed consent. Safety data were reviewed by an independent data monitoring committee. All manuscript drafts were prepared by the authors with editorial assistance funded by the sponsor. All authors approved the submission and vouched for data accuracy and completeness.

Results

Patients

A total of 1021 patients were enrolled at 317 study sites across 26 countries between June 2015 and March 2017 and comprised the ITT population. Patients were randomized 1:1:1 to receive A+CP (n = 338), A+CnP (n = 343), or CnP (n = 340) (Supplementary Fig. 1). The clinical cutoff date (CCOD) was January 22, 2018, for the primary PFS analysis and October 3, 2018, for the final OS analysis. Overall, 82% of patients (n = 835) were male, 92% (n = 935) were current or previous smokers, 33% (n = 334) had a baseline ECOG PS of 0, and 67% (n = 685) had a baseline ECOG PS of 1 (Table 1). The median age was 65 years (range, 23–86). One patient in the A+CnP arm had an *EGFR* mutation; for all other patients, the *EGFR* mutation and *ALK* rearrangement status were either negative or unknown. In the A+CP arm, 48 (14.2%), 120 (35.5%), and 170 patients (50.3%) had tumors with high (TC3 or IC3), low (TC1/2 or IC1/2), and negative (TC0 and IC0) PD-L1 expression, respectively. A total of 47 (13.7%), 136 (39.7%), and 160 patients (46.6%) in the A+CnP arm and 44 (12.9%), 125 (36.8%), and 171 patients (50.3%) in the CnP arm had tumors with high, low, and negative PD-L1 expression, respectively.

PFS Analysis

At primary CCOD (January 22, 2018), median follow-up was 18.1 months in the A+CnP arm and 16.1 months in the CnP arm. In the ITT population, 270 patients (78.7%) in the A+CnP arm and 289 patients (85.0%) in the CnP arm had a PFS event per investigator assessment. PFS benefit was found with A+CnP versus CnP in the ITT population (stratified HR = 0.71, 95% CI: 0.60–0.85; $p = 0.0001$) (Fig. 1*A*), with a median PFS of 6.3 months (95% CI: 5.7–7.1) in the A+CnP arm and 5.6 months (95% CI: 5.5–5.7) in the CnP arm. The 12-month PFS rate was 24.7% in the A+CnP arm versus 12.0% in the CnP arm. The PFS in the clinical subgroups within the ITT population is reported in Supplementary Figure 3. The PFS according to PD-L1 expression status and Teff gene signature is presented in Table 2. Although the PFS in the PD-L1 expression subgroups was not formally tested, patients whose tumors had the highest PD-L1 expression level (TC3 or IC3) had a more pronounced benefit with A+CnP than those treated with CnP did (median PFS was 10.1 versus 5.1 mo in the A+CnP versus CnP arms; HR = 0.41; 95% CI: 0.25–0.68). PFS in the ITT population assessed by an independent review facility resulted in a median PFS of 6.9 months in the A+CnP arm and 5.7 months in the CnP arm (stratified HR = 0.80, 95% CI: 0.67–0.96) (Supplementary Fig. 5). Updated investigator-assessed PFS for the ITT population with a CCOD of October 3, 2018, is shown in the supplementary data (Supplementary Fig. 6).

OS Analysis

At the final OS analysis (CCOD: October 3, 2018), median follow-up was 26.8 months in the A+CnP arm and 24.8 months in the CnP arm. There were 228 (66.5%) and 245 (72.1%) deaths in the A+CnP and CnP arms, respectively. Median OS in the ITT population was similar between the A+CnP and CnP arms: 14.2 months (95% CI: 12.3–16.8) and 13.5 months (95% CI: 12.2–15.1), respectively (stratified HR = 0.88, 95% CI: 0.73–1.05; $p = 0.1581$) (Fig. 1B, Supplementary Fig. 4). At 24 months, 32.5% and 26.6% of patients in the A+CnP and CnP arms, respectively, were alive. OS in the clinical subgroups within the ITT population is reported in Supplementary Figure 4. OS according to PD-L1 expression status and Teff gene signature is presented in Table 3. In the high PD-L1 expression subgroup (TC3 or IC3), median OS was 23.4 months in the A+CnP arm versus 10.2 months in the CnP arm (HR = 0.48, 95% CI: 0.29–0.81) (Table 3). As the OS boundary for significance was not crossed between the A+CnP and CnP arms in the ITT population, PFS and OS were not formally tested between the A+CP and CnP arms.

After discontinuation of study treatment, 124 patients (36.2%) in the A+CnP arm and 198 patients (58.2%) in the CnP arm received subsequent anticancer therapies (Supplementary Table 2). In the A+CnP arm, 110 patients (32.1%) received subsequent chemotherapy and 22 patients (6.4%) received subsequent cancer immunotherapy. In the CnP arm, 93 patients (27.4%) received subsequent chemotherapy and 147 patients (43.2%) received subsequent cancer

Table 1. Baseline Demographics and Characteristics of the ITT Population[a]

Characteristic	ITT		
	A+CP (n = 338)	A+CnP (n = 343)	CnP (n = 340)
Median age (range), y	66 (43-85)	65 (23-83)	65 (38-86)
Age groups (y), n (%)			
<65	150 (44.4)	170 (49.6)	156 (45.9)
65-74	148 (43.8)	134 (39.1)	145 (42.6)
75-84	39 (11.5)	39 (11.4)	38 (11.2)
≥85	1 (0.3)	0	1 (0.3)
Male, n (%)	278 (82.2)	280 (81.6)	277 (81.5)
Liver metastases present at enrollment (IxRS), n (%)	66 (19.5)	70 (20.4)	69 (20.3)
Ethnic origin, n (%)			
White	290 (85.8)	289 (84.3)	290 (85.3)
Asian	34 (10.1)	41 (12.0)	37 (10.9)
Black or African American	3 (0.9)	4 (1.2)	7 (2.1)
American Indian or Alaska Native	3 (0.9)	1 (0.3)	1 (0.3)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
Multiple	1 (0.3)	6 (1.7)	1 (0.3)
Unknown	6 (1.8)	2 (0.6)	4 (1.2)
ECOG PS, n (%)			
0	109 (32.2)	115 (33.5)	110 (32.4)
1	229 (67.8)	227 (66.2)	229 (67.4)
Unknown	0	1 (0.3)	1 (0.3)
Tobacco use history, n (%)			
Never smoker	30 (8.9)	32 (9.3)	23 (6.8)
Current or previous smoker	308 (91.1)	311 (90.7)	316 (92.9)
Unknown	0	0	1 (0.3)
Teff populations, n (%)[b]			
Low	185 (54.7)	189 (55.1)	175 (51.5)
High	123 (36.4)	124 (36.2)	147 (43.2)
Unknown	30 (8.9)	30 (8.7)	18 (5.3)
PD-L1 expression subgroups, n (%)[c]			
TC3 or IC3	48 (14.2)	47 (13.7)	44 (12.9)
TC2/3 or IC2/3	100 (29.6)	115 (33.5)	108 (31.8)
TC 1/2/3 or IC1/2/3	167 (49.4)	182 (53.1)	169 (49.7)
TC1/2 or IC1/2	120 (35.5)	136 (39.7)	125 (36.8)
TC0 and IC0	170 (50.3)	160 (46.6)	171 (50.3)

[a]CCOD: October 03, 2018.
[b]Teff high, T-effector signature score greater than or equal to −1.91; Teff low, T-effector signature score less than −1.91.
[c]TC3 or IC3 (high) = PD-L1 expression on greater than or equal to 50% of TC or greater than or equal to 10% of IC; TC2/3 or IC2/3 = PD-L1 expression on greater than or equal to 5% of TC or IC; TC1/2/3 or IC1/2/3 (positive) = PD-L1 expression on greater than or equal to 1% of TC or IC; TC1/2 or IC1/2 (low) = PD-L1 expression on greater than or equal to 1% of TC or IC and less than 50% of TC and less than 10% of IC; TC0 and IC0 (negative) = PD-L1 expression on less than 1% of TC and IC.
A+CnP, atezolizumab+carboplatin+nab-paclitaxel; A+CP, atezolizumab+carboplatin+paclitaxel; CCOD, clinical cutoff date; CnP, carboplatin+nab-paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cells; ITT, intention-to-treat; PD-L1, programmed death-ligand 1; Teff, T-effector; TC, tumor cells.

immunotherapy. In both arms, nivolumab was the most frequently administered cancer immunotherapy after the end of study treatment (Supplementary Table 2).

OS data from the first (CCOD: January 22, 2018) and second (CCOD: April 20, 2018) interim analyses are included in the supplementary data (Supplementary Figs. 7 and 8).

ORR and DOR

At the final CCOD (October 3, 2018), confirmed investigator-assessed ORR in the ITT population was 49.7% in the A+CnP arm and 41.0% in the CnP arm, with a median DOR of 7.3 months (95% CI: 6.8–9.5) and 5.2 months (95% CI: 4.4–5.6), respectively (Supplementary Table 3). A total of 37 patients (21.8%) in the A+CnP arm and 16 patients (11.5%) in the CnP arm had ongoing responses at the time of clinical cutoff. Overall, ORR and DOR at the final analysis were consistent with those from the primary analysis[17] (January 22, 2018). In the subgroup of patients with high PD-L1 expression (TC3 or IC3), ORR was 61.7% with A+CnP and 31.8% with CnP, and median DOR was 13.6 and 5.5

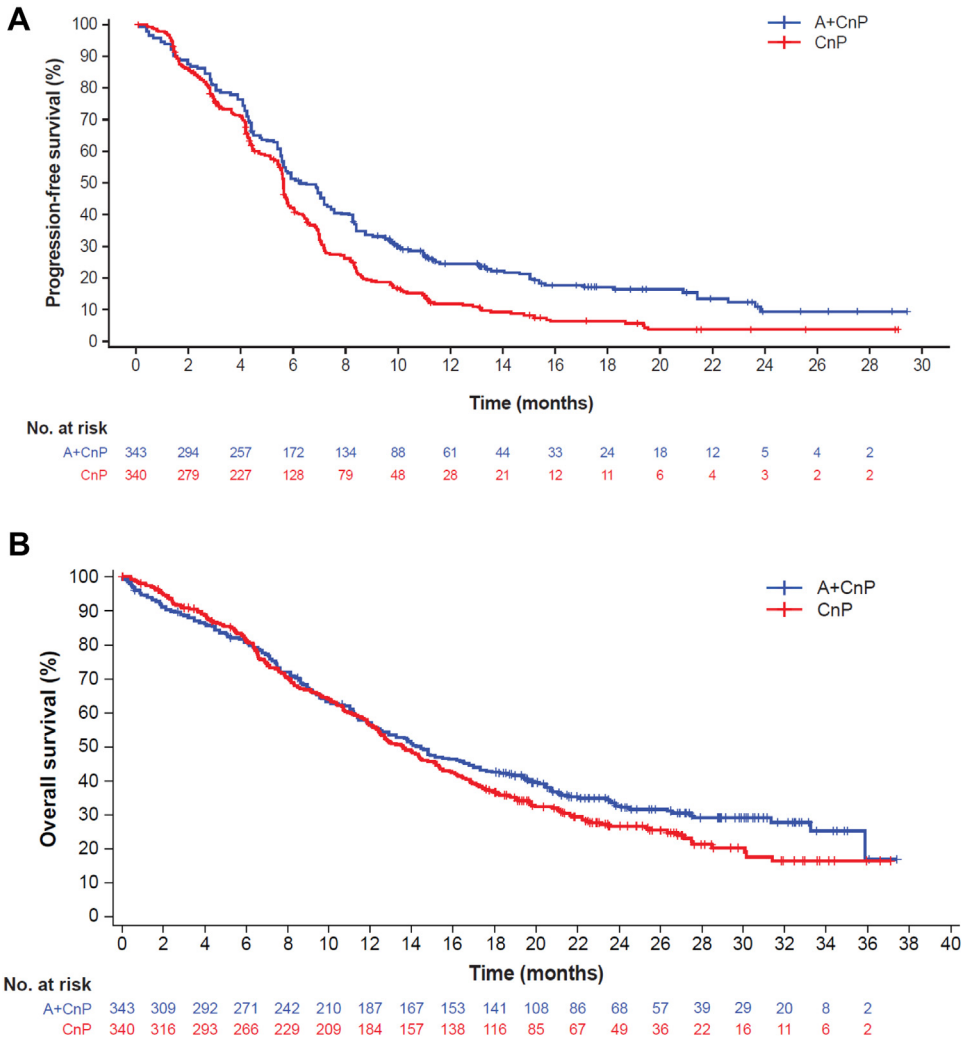

Figure 1. Investigator-assessed PFS and OS in the ITT population. (*A*) Kaplan-Meier estimates of PFS at the primary analysis (CCOD: January 22, 2018). (*B*) Kaplan-Meier estimates of OS at the final analysis (CCOD: October 3, 2018). A+CnP, atezolizumab+carboplatin+nab-paclitaxel; CCOD, clinical cutoff date; CnP, carboplatin+nab-paclitaxel; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

months, respectively (Supplementary Table 3). In the PD-L1–low (TC1/2 or IC1/2) and PD-L1–negative (TC0 and IC0) subgroups, ORR was 52.6% with A+CnP and 43.5% with CnP and 43.8% with A+CnP and 41.5% with CnP, respectively.

Safety

A total of 332 patients in the A+CP arm and 334 patients each in the A+CnP and CnP arms had received any amount of study treatment and were included in the safety population. At the time of the final CCOD (October 3, 2018), the median treatment duration of atezolizumab was 5.5 months (range, 0–37) in the A+CP arm, with a median of eight cycles (range, 1–55), and 6.7 months (range, 0–37) in the A+CnP arm, with a median of 10 cycles (range, 1–51). Median carboplatin treatment duration was 2.2 months (range, 0–5) in the A+CP arm, 2.6 months (range, 0–7) in the A+CnP arm, and 2.4 months (range, 0–7) in the CnP arm. For nab-paclitaxel, the median duration of treatment was 3.0 months (range, 0–7) in the A+CnP arm and 2.8 months (range, 0–7) in the CnP arm. Median treatment duration of paclitaxel in the A+CP arm was 2.2 months (range, 0–5).

Any-cause AEs of any grade occurred in 325 patients (97.9%) in the A+CP arm, 332 patients (99.4%) in the A+CnP arm, and 324 patients (97.0%) in the CnP arm (Table 4). Any-cause serious AEs occurred in 143 patients (43.1%) in the A+CP arm, 160 patients (47.9%) in A+CnP arm, and 96 patients (28.7%) in the CnP arm. A total of 28 patients (8.4%) in the A+CP arm, 34 patients (10.2%) in the A+CnP arm, and 14 patients (4.2%) in the CnP arm had a grade 5 AE of any cause. The higher incidence of serious AEs observed in the atezolizumab-containing arms was mainly driven by respiratory,

Table 2. Investigator-Assessed PFS Among Biomarker Subgroups in the ITT Population at Primary Analysis[a]

Subgroup	Median PFS (mo) A+CnP	CnP	HR (95% CI)
Teff populations[b]			
Teff high	6.9	5.6	0.61 (0.46-0.81)
Teff low	6.0	5.7	0.84 (0.67-1.05)
PD-L1 subgroups[c]			
TC3 or IC3	10.1	5.1	0.41 (0.25-0.68)
TC2/3 or IC2/3	8.4	5.6	0.53 (0.39-0.72)
TC1/2/3 or IC1/2/3	7.1	5.6	0.61 (0.48-0.77)
TC1/2 or IC1/2	6.5	5.6	0.70 (0.54-0.91)
TC0 and IC0	5.7	5.6	0.82 (0.65-1.04)

[a]CCOD: January 22, 2018.
[b]Teff high, T-effector signature score greater than or equal to −1.91; Teff low, T-effector signature score less than −1.91.
[c]TC3 or IC3 (high) = PD-L1 expression on greater than or equal to 50% of TC or greater than or equal to 10% of IC; TC2/3 or IC2/3 = PD-L1 expression on greater than or equal to 5% of TC or IC; TC1/2/3 or IC1/2/3 (positive) = PD-L1 expression on greater than or equal to 1% of TC or IC; TC1/2 or IC1/2 (low) = PD-L1 expression on greater than or equal to 1% of TC or IC and less than 50% of TC and less than 10% of IC; TC0 and IC0 (negative) = PD-L1 expression on less than 1% of TC and IC.
A+CnP, atezolizumab+carboplatin+nab-paclitaxel; CCOD, clinical cutoff date; CI, confidence interval; CnP, carboplatin+nab-paclitaxel; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; Teff, T-effector.

Table 3. OS in Biomarker Subgroups in the ITT Population at Final Analysis[a]

Subgroup	Median OS (mo) A+CnP	CnP	HR (95% CI)
Teff populations[b]			
Teff high	17.0	15.9	0.88 (0.66-1.19)
Teff low	13.2	12.6	0.89 (0.69-1.13)
PD-L1 subgroups[c]			
TC3 or IC3	23.4	10.2	0.48 (0.29-0.81)
TC2/3 or IC2/3	20.4	14.5	0.72 (0.52-1.00)
TC1/2/3 or IC1/2/3	14.8	15.0	0.86 (0.67-1.11)
TC1/2 or IC1/2	12.8	15.5	1.08 (0.81-1.45)
TC0 and IC0	14.0	12.5	0.87 (0.67-1.13)

[a]CCOD: October 3, 2018.
[b]Teff high, T-effector signature score greater than or equal to −1.91; Teff low, T-effector signature score less than −1.91.
[c]TC3 or IC3 (high) = PD-L1 expression on greater than or equal to 50% of TC or greater than or equal to 10% of IC; TC2/3 or IC2/3 = PD-L1 expression on greater than or equal to 5% of TC or IC; TC1/2/3 or IC1/2/3 (positive) = PD-L1 expression on greater than or equal to 1% of TC or IC; TC1/2 or IC1/2 (low) = PD-L1 expression on greater than or equal to 1% of TC or IC and less than 50% of TC and less than 10% of IC; TC0 and IC0 (negative) $^{1}/_{4}$ PD-L1 expression on less than 1% of TC and IC.
A+CnP, atezolizumab+carboplatin+nab-paclitaxel; CCOD, clinical cutoff date; CI, confidence interval; CnP, carboplatin+nab-paclitaxel; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cells; Teff, T-effector.

thoracic, and mediastinal disorders (A+CP, 15.7%; A+CnP, 12.3%; CnP, 6.6%), particularly pneumonitis (A+CP, 3.3%; A+CnP, 3.0%; CnP, 0.6%), and by blood and lymphatic system disorders (A+CP, 6.9%; A+CnP, 7.2%; CnP, 3.9%), mainly febrile neutropenia (A+CP, 4.8%; A+CnP, 3.9%; CnP, 1.5%) and anemia (A+CP, 1.8%; A+CnP, 2.1%; CnP, 0.9%). AEs led to withdrawal of any treatment in 88 patients (26.5%) in the A+CP arm, 102 patients (30.5%) in the A+CnP arm, and 58 patients (17.4%) in the CnP arm.

Treatment-related AEs (TRAEs) of any grade occurred in 306 patients (92.2%) in the A+CP arm, 316 patients (94.6%) in the A+CnP arm, and 303 patients (90.7%) in the CnP arm (Tables 4 and 5). The most common grade 3 and 4 TRAEs (≥10% incidence in any arm) were anemia (A+CP, 9.3%; A+CnP, 22.2%; CnP, 20.7%), neutropenia (A+CP, 7.5%; A+CnP, 21.3%; CnP, 22.5%), febrile neutropenia (A+CP, 7.5%; A+CnP, 5.4%; CnP, 2.1%), thrombocytopenia (A+CP, 4.2%; A+CnP, 9.3%; CnP, 8.1%), and decreased neutrophil count (A+CP, 4.8%; A+CnP, 10.8%; CnP, 13.8%) (Table 5). Serious TRAEs occurred in 77 patients (23.2%) in the A+CP arm, 70 patients (21.0%) in the A+CnP arm, and 35 patients (10.5%) in the CnP arm (Table 4 and Supplementary Table 4). The most common grade 3 and 4 serious TRAEs (≥2% incidence in any arm) were febrile neutropenia (A+CP, 4.5%; A+CnP, 3.9%; CnP, 1.5%) and pneumonitis (A+CP, 2.4%; A+CnP, 0.9%; CnP, 0.6%) (Supplementary Table 4). Nine patients (2.7%) in the A+CP arm, four patients (1.2%) in the A+CnP arm, and three patients (0.9%) in the CnP arm had treatment-related grade 5 AEs (Supplementary Table 5).

Most immune-related AEs were grade 1 and 2 in all the treatment arms. The most common immune-related AEs (≥5% incidence in any arm) were rash (A+CP, 24.7%; A+CnP, 23.1%; CnP, 11.7%), abnormal hepatic function (A+CP, 16.9%; A+CnP, 17.7%; CnP, 8.1%), hypothyroidism (A+CP, 10.5%; A+CnP, 11.1%; CnP, 0.9%), and pneumonitis (A+CP, 7.5%; A+CnP, 7.5%; CnP, 1.5%) (Supplementary Table 6). Two patients in the A+CP arm experienced a grade 5 immune-related AE: one case of Guillain-Barré syndrome and one of pneumonitis. In the A+CnP arm, one patient had a grade 5 immune-related AE of abnormal hepatic function.

Discussion

IMpower131 met its coprimary end point of investigator-assessed PFS in the ITT population (median PFS: A+CnP, 6.3 mo versus CnP, 5.6 mo; stratified HR = 0.71; 95% CI: 0.60–0.85; $p = 0.0001$), and an enhanced PFS benefit was observed with A+CnP versus CnP in the PD-L1–high subgroup (TC3 or IC3), despite not being formally tested for treatment comparison. Median OS in the ITT population was similar between the A+CnP (14.2 mo) and CnP (13.5 mo) arms (stratified HR = 0.88, 95% CI: 0.73–1.05; $p = 0.1581$). Of note, a higher

Table 4. Safety Summary[a]

	A+CP (n = 332)	A+CnP (n = 334)	CnP (n = 334)
Median treatment duration (range), mo			
Atezolizumab	5.5 (0-37)	6.7 (0-37)	NA
Carboplatin	2.2 (0-5)	2.6 (0-7)	2.4 (0-7)
Nab-paclitaxel	NA	3.0 (0-7)	2.8 (0-7)
Paclitaxel	2.2 (0-5)	NA	NA
All-cause AE, n (%)	325 (97.9)	332 (99.4)	324 (97.0)
Grade 3-4	185 (55.7)	243 (72.8)	221 (66.2)
Grade 5	28 (8.4)	34 (10.2)	14 (4.2)
Treatment-related AE, n (%)[b]	306 (92.2)	316 (94.6)	303 (90.7)
Grade 3-4	146 (44.0)	227 (68.0)	192 (57.5)
Grade 5	9 (2.7)	4 (1.2)	3 (0.9)
Serious AE, n (%)	143 (43.1)	160 (47.9)	96 (28.7)
Treatment-related, n (%)[b]	77 (23.2)	70 (21.0)	35 (10.5)
AE leading to withdrawal from any treatment, n (%)[b]	88 (26.5)	102 (30.5)	58 (17.4)
AE leading to any dose modification/interruption, n (%)[b]	188 (56.6)	261 (78.1)	219 (65.6)

[a]CCOD: October 3, 2018.
[b]Incidence of treatment-related AEs, serious treatment-related AEs, and AEs leading to withdrawal from any treatment or any dose modification/interruption are for any study treatment.
A+CnP, atezolizumab+carboplatin+nab-paclitaxel; A+CP, atezolizumab+carboplatin+paclitaxel; AE, adverse event; CCOD, clinical cutoff date; CnP, carboplatin+nab-paclitaxel; NA, not applicable.

proportion of patients in the CnP arm received subsequent cancer immunotherapy than patients in the A+CnP arm. Although patients with low PD-L1 expression (TC1/2 or IC1/2) appeared to derive PFS benefit with the addition of atezolizumab (HR = 0.70, 95% CI: 0.54–0.91), this observation did not translate into an OS benefit (HR = 1.08, 95% CI: 0.81–1.45) in the A+CnP versus CnP arms in this subgroup and likely contributed to the non-significant OS result in the ITT population. This observation of OS in the PD-L1–low subgroup was

Table 5. TRAEs (Greater Than or Equal to 10% Incidence for Any Grade, Greater Than 5% Incidence for Grades 3-5)[a]

	A+CP (n = 332)			A+CnP (n = 334)			CnP (n = 334)		
Patients, n (%)	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Anemia	87 (26.2)	31 (9.3)	0	95 (28.4)	74 (22.2)	0	110 (32.9)	69 (20.7)	0
Alopecia	128 (38.6)	0	0	111 (33.2)	0	0	100 (29.9)	0	0
Neutropenia	19 (5.7)	25 (7.5)	0	45 (13.5)	71 (21.3)	0	45 (13.5)	75 (22.5)	0
Nausea	71 (21.4)	3 (0.9)	0	106 (31.7)	7 (2.1)	0	88 (26.4)	2 (0.6)	0
Fatigue	72 (21.7)	8 (2.4)	0	60 (18.0)	13 (3.9)	0	66 (19.8)	7 (2.1)	0
Thrombocytopenia	32 (9.6)	14 (4.2)	0	55 (16.5)	31 (9.3)	0	61 (18.3)	27 (8.1)	0
Decreased appetite	70 (21.1)	2 (0.6)	0	52 (15.6)	10 (3.0)	0	62 (18.6)	3 (0.9)	0
Diarrhea	58 (17.5)	6 (1.8)	0	53 (15.9)	10 (3.0)	0	56 (16.8)	7 (2.1)	0
Asthenia	48 (14.5)	10 (3.0)	0	38 (11.4)	7 (2.1)	0	44 (13.2)	9 (2.7)	0
Decreased platelet count	31 (9.3)	7 (2.1)	0	40 (12.0)	15 (4.5)	0	38 (11.4)	20 (6.0)	0
Decreased neutrophil count	3 (0.9)	16 (4.8)	0	21 (6.3)	36 (10.8)	0	19 (5.7)	46 (13.8)	0
Constipation	44 (13.3)	0	0	51 (15.3)	0	0	38 (11.4)	1 (0.3)	0
Peripheral neuropathy	58 (17.5)	7 (2.1)	0	30 (9.0)	4 (1.2)	0	30 (9.0)	2 (0.6)	0
Peripheral sensory neuropathy	52 (15.7)	2 (0.6)	0	41 (12.3)	4 (1.2)	0	29 (8.7)	1 (0.3)	0
Vomiting	34 (10.2)	1 (0.3)	0	41 (12.3)	3 (0.9)	0	39 (11.7)	1 (0.3)	0
Hypomagnesemia	20 (6.0)	0	0	33 (9.9)	5 (1.5)	0	24 (7.2)	2 (0.6)	0
Leukopenia	6 (1.8)	2 (0.6)	0	22 (6.6)	20 (6.0)	0	20 (6.0)	14 (4.2)	0
Decreased WBC count	6 (1.8)	6 (1.8)	0	15 (4.5)	14 (4.2)	0	22 (6.6)	14 (4.2)	0
Arthralgia	44 (13.3)	1 (0.3)	0	20 (6.0)	0	0	11 (3.3)	0	0
Rash	33 (9.9)	2 (0.6)	0	25 (7.5)	2 (0.6)	0	10 (3.0)	1 (0.3)	0
Myalgia	35 (10.5)	0	0	14 (4.2)	0	0	15 (4.5)	0	0
Febrile neutropenia	0	25 (7.5)	0	0	18 (5.4)	0	0	7 (2.1)	0

[a]CCOD: October 3, 2018.
A+CnP, atezolizumab+carboplatin+nab-paclitaxel; A+CP, atezolizumab+carboplatin+paclitaxel; CCOD, clinical cutoff date; CnP, carboplatin+nab-paclitaxel; TRAE, treatment-related adverse event; WBC, white blood cell.

unexpected, and further analyses are required to investigate whether an imbalance in patients' prognostic factors between arms in this subgroup could have contributed to this finding. Patients with high PD-L1 expression (TC3 or IC3) appeared to derive an OS benefit with the addition of atezolizumab (HR = 0.48, 95% CI: 0.29–0.81). Although this was encouraging, any conclusions are limited, as the study was not powered for this subgroup analysis. The treatment effect in patients with high PD-L1 expression observed in IMpower131 is consistent with previous reports of atezolizumab single or combination therapy in both first- and second-line settings of NSCLC, as reported in POPLAR, OAK, IMpower150, and the interim analysis of IMpower110.[6,7,9,14,18]

The study KEYNOTE-407 investigated pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel or chemotherapy alone in patients with stage IV squamous NSCLC who had not received previous systemic therapy for metastatic disease.[4] The addition of pembrolizumab to the chemotherapy regimen resulted in significant improvements in PFS and OS in the ITT population. As cancer immunotherapy is established as the standard of care in NSCLC, future prospective trials may address the question of whether programmed cell death protein 1 inhibition or PD-L1 inhibition results in favorable treatment outcomes, as cross-trial comparisons are inherently limited owing to the risk of systematic bias and confounding factors.

The safety profile in IMpower131 was consistent with the known safety profile of each individual treatment, and no new safety signals were observed. Serious AEs, serious TRAEs, and AEs leading to withdrawal from any treatment were higher in the atezolizumab-containing arms than in the chemotherapy-alone arm. The higher incidence of serious AEs observed in the A+CP and A+CnP arms than that observed in the CnP arm may be attributed to febrile neutropenia, anemia, and pneumonitis, a known risk with atezolizumab.

In conclusion, IMpower131 suggests that addition of atezolizumab to CnP provides PFS and OS benefit in patients with metastatic squamous NSCLC whose tumors have high PD-L1 expression.

Acknowledgments

This work was supported by F. Hoffmann-La Roche Ltd./Genentech, Inc., a member of the Roche Group. The authors acknowledge Targos Molecular Pathology GmbH (Kassel, Germany) for performing central PD-L1 and Teff gene signature testing. Medical writing assistance for this manuscript was provided by Dr. Preshita Gadkari, PhD, of Health Interactions, and funded by F. Hoffmann-La Roche, Ltd. The author contributions were as follows: conceptualization: Drs. Jotte, Vynnychenko, Huang, Hoang, Sandler, and Socinski; methodology: Drs. Vynnychenko, Huang, Hoang, McCleland, and Socinski; software: Dr. Huang; validation: Drs. Vynnychenko, Stroyakovskiy, Conter, Huang, and Sun; formal analysis: Drs. Huang, Hoang, McCleland, and Socinski; investigation: Drs. Jotte, Cappuzzo, Vynnychenko, Rodríguez-Abreu, Hussein, Soo, Conter, Graupner, Sun, Jessop, McCleland, Ballinger, and Sandler; resources: Drs. Cappuzzo, Rodríguez-Abreu, Soo, Conter, Kozuki, and Huang; data curation: Drs. Jotte, Cappuzzo, Vynnychenko, Conter, Huang, and Sun; writing—original draft: Drs. Cappuzzo, Graupner, Sun, Jessop, and Socinski; writing—review and editing: all authors; visualization: Drs. Jotte, Cappuzzo, Vynnychenko, Huang, Sun, Hoang, and Socinski; supervision: Drs. Jotte, Conter, Hoang, Ballinger, Sandler, and Socinski; project administration: Drs. Jotte, Conter, Sun, Hoang, and Socinski; funding acquisition: Dr. Conter.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.03.028.

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