

Safety and Patient-Reported Outcomes of Atezolizumab Plus Chemotherapy With or Without Bevacizumab Versus Bevacizumab Plus Chemotherapy in Non–Small-Cell Lung Cancer

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abstract

PURPOSE Atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) demonstrated survival benefit versus bevacizumab, carboplatin, and paclitaxel (BCP) in chemotherapy-naïve nonsquamous non–small-cell lung cancer (NSCLC). We present safety and patient-reported outcomes (PROs) to provide additional information on the relative impact of adding atezolizumab to chemotherapy with and without bevacizumab in nonsquamous NSCLC.

METHODS Patients were randomly assigned to receive atezolizumab, carboplatin, and paclitaxel (ACP), ABCP, or BCP. Coprimary end points were overall survival and investigator-assessed progression-free survival. The incidence, nature, and severity of adverse events (AEs) were assessed. PROs, a secondary end point, were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 and EORTC QLQ-Lung Cancer 13.

RESULTS Overall, 400 (ACP), 393 (ABCP), and 394 (BCP) patients were safety evaluable (ie, intention-to-treat population that received one or more doses of any study treatment). More patients had grade 3/4 treatment-related AEs during the induction versus maintenance phase (ACP, 40.5% v 8.2%; ABCP, 48.6% v 21.2%; BCP, 44.7% v 11.1%). During induction, the incidence of serious AEs (SAEs) was 28.3%, 28.5%, and 26.4% in the ACP, ABCP, and BCP arms, respectively. During maintenance, SAE incidences were 20.0%, 26.3%, and 13.0%, respectively. Completion rates of the PRO questionnaires were > 88% at baseline and remained ≥ 70% throughout most study visits. Across arms, patients on average reported no clinically meaningful worsening of global health status or physical functioning scores through cycle 13. Patients across arms rated common symptoms with chemotherapy and immunotherapy similarly.

CONCLUSION ABCP seems tolerable and manageable versus ACP and BCP in first-line nonsquamous NSCLC. Treatment tolerability differed between induction and maintenance phases across treatment arms. PROs reflect a minimal treatment burden (eg, health-related quality of life, symptoms) with each regimen.

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Treatment options for patients with metastatic non–small-cell lung cancer (NSCLC) have expanded with the availability of immune checkpoint inhibitor therapies,^{1,2} particularly programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1) inhibitors.³⁻⁶ In the first-line setting, these options include anti-PD-1 monotherapy in patients with PD-L1 expression on ≥ 1% of tumor cells or combination approaches of anti-PD-L1 or anti-PD-1 with platinum doublet chemotherapy with and without pemetrexed or bevacizumab.^{1,7-12} Because these combinations become more prevalent in the clinical setting, a better understanding of the safety

profiles of these agents within the combination backgrounds is needed. Symptoms at presentation as well as symptomatic adverse events (AEs) that arise from treatment, as part of the treatment burden, adversely affect health-related quality of life (HRQOL).¹³⁻¹⁵ It is therefore important to characterize a patient's overall experience to determine the net benefit of treatment combination strategies and ensure that delayed tumor progression or increased survival does not come at the expense of their HRQOL.¹⁶⁻²²

Atezolizumab (anti-PD-L1) has demonstrated overall survival (OS) benefit versus docetaxel in previously treated NSCLC, regardless of PD-L1 expression.³

CONTEXT

Key Objective

Atezolizumab in combination bevacizumab and chemotherapy is a first-line treatment option in nonsquamous non-small-cell lung cancer (NSCLC). The safety and patient-reported outcomes (PROs) data provide complementary evidence of the tolerability of this multi-regimen therapy.

Knowledge Generated

Standardized safety reporting combined with patients' ratings of the severity of commonly experienced treatment-related symptoms and health-related quality of life, confirm that adding immunotherapy (atezolizumab) to bevacizumab and chemotherapy in nonsquamous NSCLC is not adding significant treatment burden while improving survival.

Relevance

Provide additional patient-centric evidence to inform the tolerability of atezolizumab administered in combination with bevacizumab and chemotherapy as first-line treatment in nonsquamous NSCLC.

Patient-reported outcomes (PROs) also showed improved HRQOL with atezolizumab versus docetaxel in second-line NSCLC, supporting the benefit and tolerability observed with atezolizumab versus docetaxel.²³ Bevacizumab (anti-vascular endothelial growth factor [VEGF]) is an anti-angiogenic agent that also inhibits VEGF-mediated immunosuppression.²⁴ Therefore, bevacizumab may enhance the antitumor activity of atezolizumab. Atezolizumab combined with bevacizumab, carboplatin, and paclitaxel chemotherapy (ABCP) showed progression-free survival (PFS) and OS benefit versus bevacizumab, carboplatin, and paclitaxel (BCP) chemotherapy^{7,25} (PFS hazard ratio, 0.59 [95% CI, 0.50 to 0.69]; OS hazard ratio, 0.76 [95% CI, 0.63 to 0.93]; data cutoff, January 22, 2018).⁷ The combination is approved in the United States, European Union, and other regions for the first-line treatment of metastatic nonsquamous NSCLC.^{26,27} The overall safety profile of ABCP was consistent with that of the individual medicines,^{3,28} and no new safety signals were observed.⁷

We further report on the safety of atezolizumab plus carboplatin and paclitaxel (ACP), ABCP, and BCP in the IMpower150 study. PROs of HRQOL, physical functioning, and treatment-related symptoms show the relative impact of these treatment regimens.

METHODS

Study Design, Patients, and Treatment

IMpower150 is a global, open-label, randomized, phase III study.⁷ Patients were enrolled if they had chemotherapy-naïve, metastatic, nonsquamous NSCLC. Details of the study design, patient population, and treatments were previously described⁷; a brief description is included in the Data Supplement.

This study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and all patients gave written informed consent. The protocol, informed consent forms, any information provided to patients, and relevant supporting information were reviewed

and approved by the institutional review board/ethics committee.

Objective

The objective of this analysis was to evaluate the safety and tolerability of atezolizumab, as reported per standardized safety procedures and using data collected from patients on PRO rating scales for each of the two treatment comparisons (ABCP v BCP and ACP v BCP). The PRO end points aimed to capture patients' ratings of the severity of commonly experienced symptoms with these treatments and characterize their impact on HRQOL and physical functioning.

Safety and PRO Assessments

All-cause AEs, treatment-related AEs (TRAEs; related to any study treatment or individual study treatments), and AEs of special interest (AESIs) were assessed. The incidence, nature, and severity of these events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Atezolizumab AESIs were defined as important identified risks, potential risks, and class effects that have been associated with atezolizumab and other immune checkpoint inhibitors, including immune-related AEs (irAEs) and infusion-related reactions. The irAEs were defined using Medical Dictionary for Regulatory Activities Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. Post hoc safety analyses included the incidence, nature, and severity of AEs reported by treatment phase (induction v maintenance); time to onset and duration of irAEs; and TRAE rates that led to treatment discontinuation. For analysis of AEs by treatment phase, AEs that occurred during induction had an onset on or after the first study drug treatment and up to 1 day before the date of the first dose of the maintenance therapy, and AEs that occurred during maintenance had an onset on or after the first dose of maintenance therapy.

TABLE 1. Baseline Patient Characteristics

Characteristic	Safety-Evaluable Intention-to-Treat Patients, No. (%)			
	ACP (n = 400) ^a	ABCP (n = 393)	BCP (n = 394)	All (N = 1,187)
Age, years				
Median	63.0	63.0	63.0	63.0
Range	32-85	31-89	31-90	31-90
Sex				
Male	238 (59.5)	239 (60.8)	233 (59.1)	710 (59.8)
Race				
White	329 (82.3)	316 (80.4)	329 (83.5)	974 (82.1)
Asian	48 (12.0)	55 (14.0)	46 (11.7)	149 (12.6)
Black	9 (2.3)	3 (0.8)	12 (3.0)	24 (2.0)
American Indian or Alaska Native	0	3 (0.8)	1 (0.3)	4 (0.3)
Multiple	4 (1.0)	3 (0.8)	0	7 (0.6)
Unknown	10 (2.5)	13 (3.3)	6 (1.5)	29 (2.4)
ECOG performance status ^b				
0	179 (44.8)	158 (40.5)	177 (45.3)	514 (43.3)
1	221 (55.3)	232 (59.5)	214 (54.7)	667 (56.2)
Tobacco use history				
Never	77 (19.3)	80 (20.4)	76 (19.3)	233 (19.6)
Current/previous	323 (80.7)	313 (79.6)	318 (80.7)	954 (80.4)
Liver metastases at enrollment				
Absent	333 (83.3)	330 (84.0)	327 (83.0)	990 (83.4)
Present	67 (16.8)	63 (16.0)	67 (17.0)	197 (16.6)
EGFR mutation status				
Positive	44 (11.0)	33 (8.4)	44 (11.2)	121 (10.2)
Negative	347 (86.8)	347 (88.3)	342 (86.8)	1,036 (87.3)
Unknown	9 (2.3)	13 (3.3)	8 (2.0)	30 (2.5)
PD-L1 subgroup ^c				
TC3 or IC3	68 (17.0)	74 (18.8)	72 (18.3)	214 (18.0)
TC1/2 or IC1/2	148 (37.1)	132 (33.6)	126 (32.0)	407 (34.3)
TC0 and IC0	183 (45.9)	187 (47.6)	196 (49.7)	566 (47.7)

NOTE. TC3 or IC3 is defined as PD-L1 expression on $\geq 50\%$ of TCs or $\geq 10\%$ of ICs; TC1/2 or IC1/2 is defined as PD-L1 expression on $\geq 1\%$ and $< 50\%$ of TCs or $\geq 1\%$ and $< 10\%$ of ICs; and TC0 or IC0 is defined as PD-L1 expression on $< 1\%$ of TCs and ICs.

Abbreviations: ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; BCP, bevacizumab, carboplatin, and paclitaxel; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cell; PD-L1, programmed death-ligand 1; TC, tumor cell.

^aOne patient in the ABCP arm never received bevacizumab in error and is therefore counted as part of the safety population in the ACP arm.

^bThree patients in the ABCP arm and three patients in the BCP arm had missing data at baseline.

^cOne patient in the ACP arm had missing data at baseline.

PROs were assessed using validated and reliable self-report measures: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 (C30)^{29,30} and the EORTC QLQ-Lung Cancer 13 (LC13).³¹ The EORTC QLQ-C30 consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global

health/QOL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC QLQ-LC13 module, which assesses the severity of lung cancer-specific symptoms, incorporates one multiple-item scale to assess dyspnea and a series of single items that assess pain, cough, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Questionnaires were completed at each scheduled study

TABLE 2. Duration of Individual Study Treatments

Duration	Treatment, No. (%)		
	ACP (n = 400) ^a	ABCP (n = 393)	BCP (n = 394)
Atezolizumab exposure			
Median treatment duration, months (range)	6.4 (0-29)	8.3 (0-30)	—
Treatment duration, months	n = 400	n = 393	—
0 to ≤ 3	98 (24.5)	86 (21.9)	—
> 3 to ≤ 6	86 (21.5)	53 (13.5)	—
> 6 to ≤ 12	106 (26.5)	112 (28.5)	—
> 12	110 (27.5)	142 (36.1)	—
Median No. of doses received (range)	10 (1-43)	12 (1-44)	—
Bevacizumab exposure			
Median treatment duration, months (range)	—	6.7 (0-30)	5.1 (0-26)
Treatment duration, months	—	n = 393	n = 393
0 to ≤ 3	—	112 (28.5)	124 (31.6)
> 3 to ≤ 6	—	61 (15.5)	101 (25.7)
> 6 to ≤ 12	—	103 (26.2)	105 (26.7)
> 12	—	117 (29.8)	63 (16.0)
Median No. of doses received (range)	—	10 (1-44)	8 (1-38)
Carboplatin exposure			
Median treatment duration, months (range)	2.1 (0-5)	2.2 (0-5)	2.2 (0-5)
Treatment duration, months	n = 399	n = 393	n = 393
0 to ≤ 3	283 (70.9)	277 (70.5)	279 (71.0)
> 3 to ≤ 6	116 (29.1)	116 (29.5)	114 (29.0)
Doses received	n = 399	n = 393	n = 393
1-3	84 (21.1)	78 (19.8)	75 (19.1)
4-5	212 (53.1)	209 (53.2)	218 (55.5)
6	103 (25.8)	106 (27.0)	100 (25.4)
Paclitaxel exposure			
Median treatment duration (range), months	2.1 (0-5)	2.2 (0-5)	2.2 (0-5)
Treatment duration, months	n = 399	n = 393	n = 394
0 to ≤ 3	287 (71.9)	279 (71.0)	285 (72.3)
> 3 to ≤ 6	112 (28.1)	114 (29.0)	109 (27.7)
Doses received	n = 399	n = 393	n = 394
1-3	90 (22.6)	85 (21.6)	81 (20.6)
4-5	210 (52.6)	206 (52.4)	217 (55.1)
6	99 (24.8)	102 (26.0)	96 (24.4)

Abbreviations: ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; BCP, bevacizumab, carboplatin, and paclitaxel.

^aOne patient in the ABCP arm never received bevacizumab in error and is therefore counted as part of the safety population in the ACP arm.

visit during treatment and 3 and 6 months after disease progression or until loss of clinical benefit in atezolizumab-treated patients who had continued treatment with atezolizumab after radiographic disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). Patients recorded their answers to the PRO questionnaires before any meaningful medical discussion

or test to minimize assessment bias. Completion took approximately 15 minutes per EORTC QLQ module. Sites did not have access to patients' answers and were not expected to use PRO information in discussions with patients about their treatment or health status. Answers were recorded on an electronic device (ePRO tablet), and data were transmitted automatically to a centralized database at the ePRO

TABLE 3. Safety Summary by Treatment Phase

AE ^b	Treatment Phase, No. (%)					
	ACP ^a		ABCP		BCP	
	Induction ^c (n = 400)	Maintenance ^d (n = 305)	Induction ^c (n = 393)	Maintenance ^d (n = 312)	Induction ^c (n = 394)	Maintenance ^d (n = 270)
≥ 1 AEs	382 (95.5)	260 (85.2)	380 (96.7)	289 (92.6)	389 (98.7)	219 (81.1)
Grade 3/4	199 (49.8)	68 (22.3)	211 (53.7)	115 (36.9)	204 (51.8)	61 (22.6)
Grade 5 ^e	6 (1.5)	4 (1.3)	15 (3.8)	8 (2.6)	11 (2.8)	9 (3.3)
≥ 1 TRAEs	365 (91.3)	172 (56.4)	362 (92.1)	221 (70.8)	375 (95.2)	147 (54.4)
Grade 3/4	162 (40.5)	25 (8.2)	191 (48.6)	66 (21.2)	176 (44.7)	30 (11.1)
Grade 5 ^f	1 (0.3)	3 (1.0)	10 (2.5)	1 (0.3)	5 (1.3)	3 (1.1)
≥ 1 SAEs	113 (28.3)	61 (20.0)	112 (28.5)	82 (26.3)	104 (26.4)	35 (13.0)
≥ 1 AESIs ^g	129 (32.3)	102 (33.4)	129 (32.8)	118 (37.8)	84 (21.3)	36 (13.3)
Grade 3/4	27 (6.8)	12 (3.9)	29 (7.4)	20 (6.4)	12 (3.0)	1 (0.4)
Grade 5	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; AE, adverse event; AESI, adverse event of special interest; BCP, bevacizumab, carboplatin, and paclitaxel; SAE, serious adverse event; TRAE, treatment-related adverse event.

^aOne patient in the ABCP arm never received bevacizumab in error and is therefore counted as part of the safety population in the ACP arm.

^bMultiple occurrences of the same AE in one individual are counted once at the highest grade for this patient in each treatment phase.

^cAEs that occurred during the induction phase had an onset on or after the first study drug treatment and up to 1 day before the date of the first dose of the maintenance therapy.

^dAEs that occurred during the maintenance phase had an onset on or after the first dose of maintenance therapy.

^eOne patient in the ABCP arm and one patient in the BCP arm had a grade 5 AE during the protocol reporting period > 30 days after having received the last dose of induction therapy and no maintenance therapy; these patients are not captured in this table.

^fOne patient in the BCP arm had a grade 5 TRAE with onset during the protocol reporting period > 30 days after having received the last dose of induction therapy and no maintenance therapy; this patient is not captured in this table.

^gAESIs include immune-related AEs and infusion-related reactions.

vendor through a prespecified transmission method (eg, web or wireless) and could be accessed by appropriate study personnel securely through the Internet. PROs were analyzed as a change from baseline in mean scores. A ≥ 10-point score change from baseline within a patient was considered the threshold of clinically meaningful change.³² The PRO and safety data were elicited per different standardized processes; therefore, no attempt was made to reconcile the two data sets.³³

Statistical Analysis

All PRO scores were derived according to developers' guidelines. Missing scores were not imputed. Descriptive analyses were conducted on the safety population per treatment received to complement traditional safety reporting and to quantify treatment and symptom burden from the patients' perspective. The most frequent and clinically relevant disease-related symptoms according to patients with NSCLC (eg, cough, chest pain, dyspnea) were examined in the safety population because these symptoms might not be solely attributed to tumor growth and, therefore, are part of the symptom burden. Other symptom ratings provided insight into patients' experiences with fatigue, nausea/vomiting, constipation, diarrhea, sore mouth, and

neuropathic pain. Mean changes from baseline in patient-reported HRQOL, physical functioning, treatment-related symptoms, and lung cancer-related symptoms were analyzed descriptively at each cycle on treatment. For selected scales, changes from baseline are presented for the induction and maintenance phases. Good practices for reporting and analyzing PROs were followed.³⁴

RESULTS

Patients and Treatment

Overall, 1,202 patients were enrolled, and 402, 400, and 400 patients were randomly assigned to receive ACP, ABCP, and BCP, respectively (Data Supplement). The data cutoff date for this analysis was January 22, 2018; the minimum duration of follow-up was 13.5 months (median, 19.6, 19.6, and 19.7 months for ACP, ABCP, and BCP, respectively).

Safety

Baseline characteristics were well-balanced across treatment arms in the safety-evaluable intention-to-treat population, which included randomly assigned patients who received any amount of any component of study treatment (Table 1). For the safety analyses, patients were grouped according to whether any amount of atezolizumab was

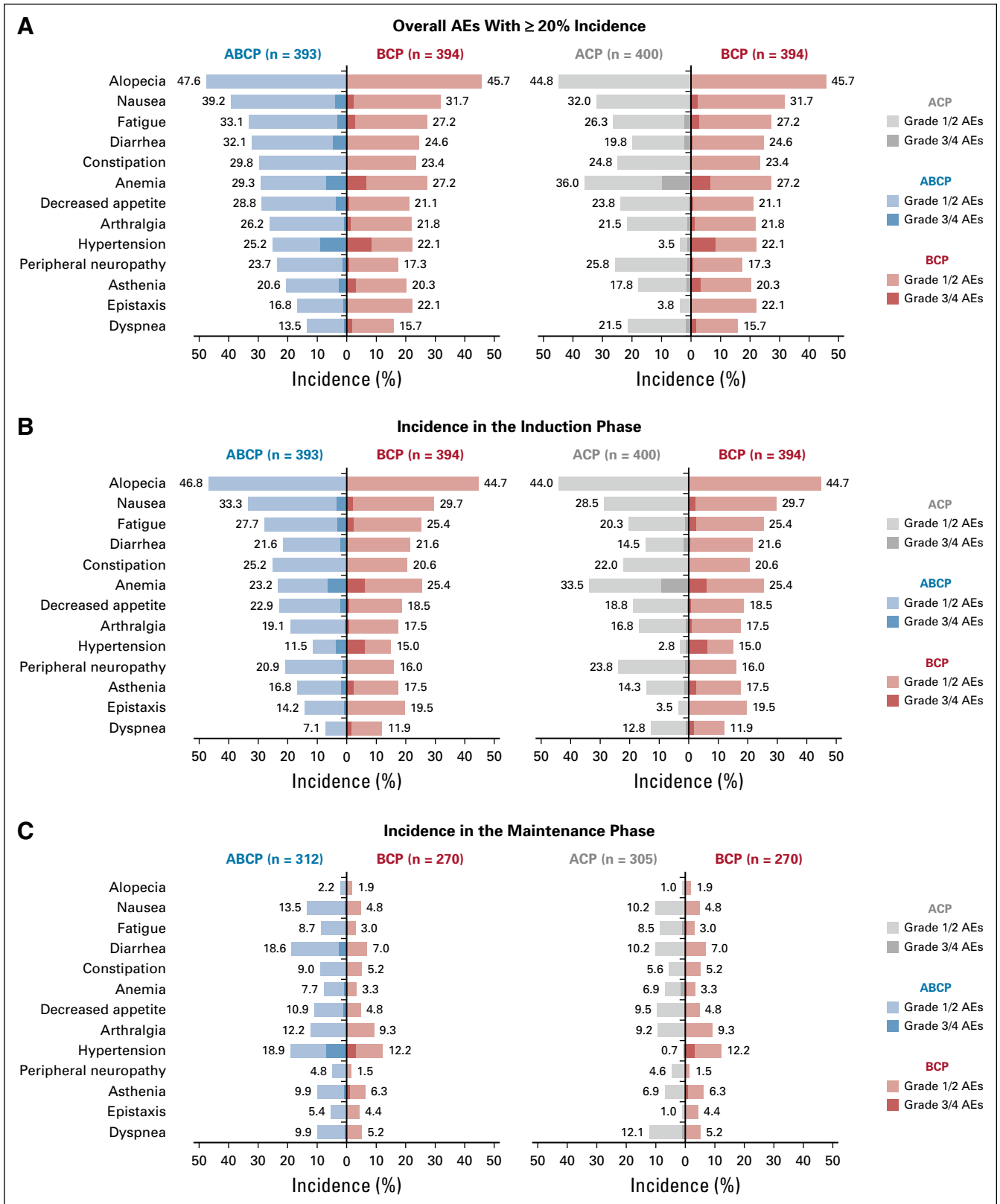


FIG 1. Most common adverse events (AEs) overall and by phase of treatment. (A) Incidences of the most common ($\geq 20\%$ overall incidence) AEs reported in any treatment arm. Incidences of the most common AEs in the (B) induction and (C) maintenance phases. AEs that occurred during the induction phase had an onset on or after the first study drug treatment and up to 1 day before the date of the first dose of the maintenance therapy. AEs that occurred during the maintenance phase had an onset on or after the first dose of maintenance therapy. Overall AEs represent (continued on following page)

received, including when it was received in error. This population comprised 400 patients treated with ACP, 393 treated with ABCP, and 394 treated with BCP. The median duration of treatment with each individual study treatment is listed in [Table 2](#).

The incidences of all-cause AEs, TRAEs, and serious AEs (SAEs) by treatment phase are listed in [Table 3](#). A higher incidence of grade 3/4 all-cause and TRAEs was observed during the induction versus maintenance phase across all treatment arms. While the incidence of grade 5 all-cause AEs was similar across treatment phases in all arms, the incidence of grade 5 TRAEs was higher during the induction versus maintenance phase in the ABCP arm. Incidence of grade 3/4 and grade 5 atezolizumab-related AEs was comparable across the ACP and ABCP arms (Data Supplement); a similar observation was noted for bevacizumab-related AEs in the ABCP and BCP arms.

The majority of the most common AEs ($\geq 20\%$ overall incidence in any arm) reported across treatment phases were grade 1/2 ([Fig 1A](#)). Alopecia, nausea, and fatigue were the most common AEs reported during the induction phase in the ABCP arm, while alopecia, anemia, nausea, and peripheral neuropathy were the most common AEs reported during this phase in the ACP arm ([Fig 1B](#)). Hypertension was the most commonly reported AE during the maintenance phase in both the ABCP and the BCP arms, while dyspnea was the most common AE reported during this phase in the ACP arm ([Fig 1C](#)). The most common bleeding/hemorrhage AESIs with bevacizumab were epistaxis (ACP, 3.8%; ABCP, 16.8%; BCP, 22.1%), hemoptysis (ACP, 3.5%; ABCP, 6.9%; BCP, 5.1%), and hematuria (ACP, 2.8%; ABCP, 3.3%; BCP, 1.8%). The majority of these events were grade 1/2 and were consistent with the known safety profile of bevacizumab.

The incidence of SAEs was higher during the induction versus maintenance phase across all arms ([Table 3](#)). During induction, the incidence of SAEs was 28.3%, 28.5%, and 26.4% in the ACP, ABCP, and BCP arms, respectively. During maintenance, SAE incidences were 20.0%, 26.3% and 13.0%, respectively. The most common SAEs ($\geq 2\%$ overall incidence in any arm) are shown in the Data Supplement. The rate of these SAEs decreased from the induction to the maintenance phase of treatment; however, the incidences of diarrhea, pneumonia, and pneumonitis in the ABCP arm were similar across treatment phases.

The overall incidence of AEs leading to discontinuation of any study treatment was 13.3% with ACP, 33.8% with

ABCP, and 24.9% with BCP. Discontinuation of only carboplatin and paclitaxel because of AEs occurred in 3.3%, 6.1%, and 6.1% of patients in the ACP, ABCP, and BCP arms, respectively. During induction, the incidence of AEs that led to discontinuation of any study treatment was higher with ABCP (22.4%) and BCP (17.8%) than with ACP (9.5%). The most commonly reported AEs that led to any treatment discontinuation during induction ($\geq 1\%$ of patients) were peripheral sensory neuropathy (ACP, 1.0%; ABCP, 2.0%; BCP, 1.0%), peripheral neuropathy (ACP, 1.0%; ABCP, 1.8%; BCP, 0.8%), pulmonary embolism (ACP, 0%; ABCP, 1.3%; BCP, 1.3%), thrombocytopenia (ACP, 0%; ABCP, 1.0%; BCP, 1.0%), and febrile neutropenia (ACP, 0%; ABCP, 0.5%; ACP, 1.0%). During maintenance, the incidence of AEs that led to discontinuation of any treatment was higher with ABCP than with BCP or ACP. The most commonly reported events that led to any treatment discontinuation during maintenance ($\geq 1\%$ of patients) were proteinuria (ACP, 0%; ABCP, 2.9%; BCP, 2.6%), hypertension (ACP, 0%; ABCP, 1.9%; BCP, 0%), increased ALT (ACP, 0%; ABCP, 1.0%; BCP, 0%), and diarrhea (ACP, 0%; ABCP, 1.0%; BCP, 0%). Atezolizumab discontinuation because of AEs during the induction and maintenance phases occurred in 7.6% and 8.3% of patients in the ABCP arm and 4.5% and 4.6% in the ACP arm, respectively. The most common event that led to atezolizumab discontinuation ($\geq 1\%$ of patients) was pneumonitis in both the induction (ACP, 1.0%; ABCP, 1.0%) and the maintenance (ACP, 1.0%; ABCP, 0.6%) phases. Bevacizumab discontinuation because of AEs in either phase occurred in 13.5% and 13.1% of patients in the ABCP arm and 11.4% and 9.3% in the BCP arm, respectively. The most common events that led to bevacizumab discontinuation during induction ($\geq 1\%$ of patients) were pulmonary embolism (ABCP, 1.3%; BCP, 1.3%) and hemoptysis (ABCP, 1.0%; BCP, 0%); during maintenance, the most common events were proteinuria (ABCP, 2.9%; BCP, 2.6%) and hypertension (ABCP, 0%; BCP, 1.9%).

The incidence of atezolizumab AESIs was similar between treatment phases in the ACP and ABCP arms, and most were grade 1/2 ([Table 3](#)). The AESI of hepatitis was divided into two categories: AEs of liver-related abnormal investigations (hepatitis laboratory abnormalities) and AEs of noninfectious hepatitis, hepatic failure, cirrhosis, and liver damage-related conditions (hepatitis diagnosis). The most common irAEs ($\geq 1\%$ overall incidence in any arm) were rash, hypothyroidism, and hepatitis laboratory abnormalities (Data Supplement). The incidence of irAEs was similar across treatment phases in the ACP and ABCP arms,

FIG 1. (continued) the sum of AEs with onset during the induction phase, the maintenance phase, and/or the AE reporting period. The AE reporting period includes those patients who discontinued induction therapy, never received maintenance therapy, and had an AE with onset > 30 days after the last dose of study treatment and during the AE reporting period as defined in the protocol. ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; BCP, bevacizumab, carboplatin, and paclitaxel.

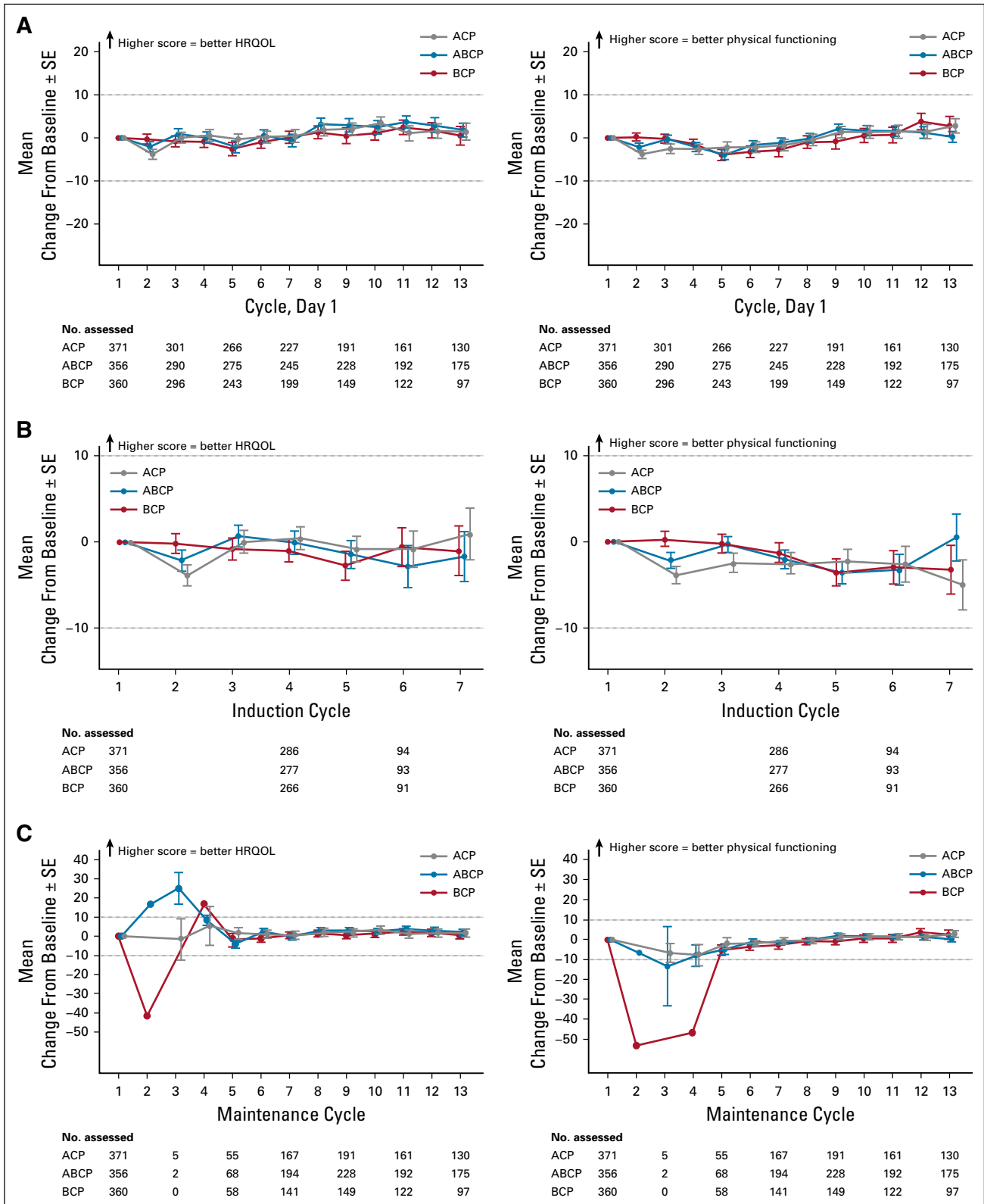


FIG 2. Mean change in baseline score of patient-reported health-related quality of life (HRQOL) and physical functioning overall and by phase of treatment. (A) Mean change in baseline scores for global health status and physical functioning overall and during the (B) induction and (C) maintenance phases. Induction was defined as four or six 21-day cycles of atezolizumab plus bevacizumab, carboplatin, and paclitaxel (ABCP); atezolizumab, carboplatin, and paclitaxel (ACP); or bevacizumab, carboplatin, and paclitaxel (BCP). Maintenance started at cycle 4 or 6, with 21-day cycles of atezolizumab plus bevacizumab (in the ABCP arm), atezolizumab (in the ACP arm), or bevacizumab (in the BCP arm).

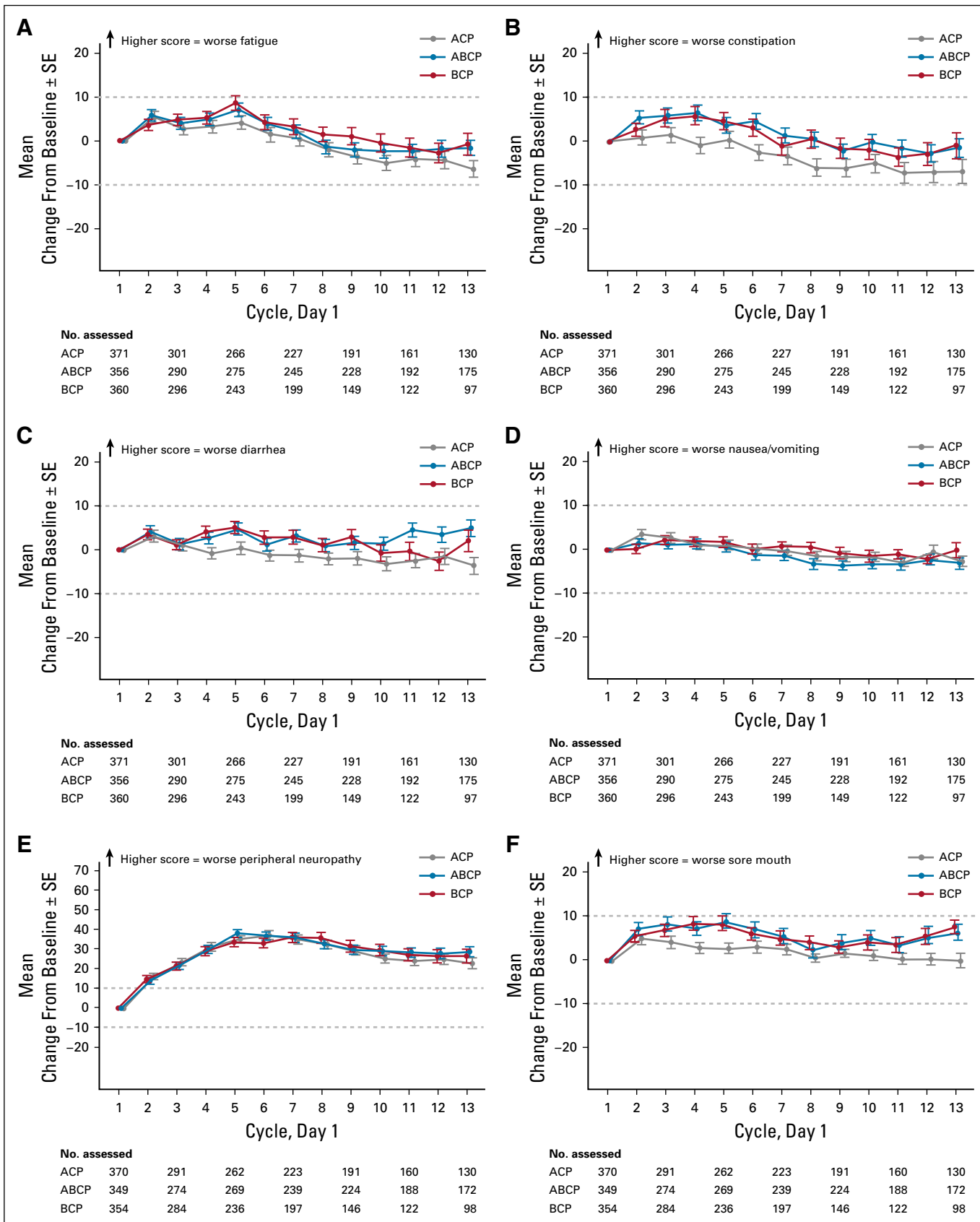


FIG 3. Mean change in baseline scores of patient-reported symptom severity. Mean change in baseline score through cycle 13 for (A) fatigue, (B) constipation, (C) diarrhea, (D) nausea/vomiting, (E) peripheral neuropathy, (F) sore mouth, (G) coughing, (H) chest pain, and (I) dyspnea. ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; BCP, bevacizumab, carboplatin, and paclitaxel.

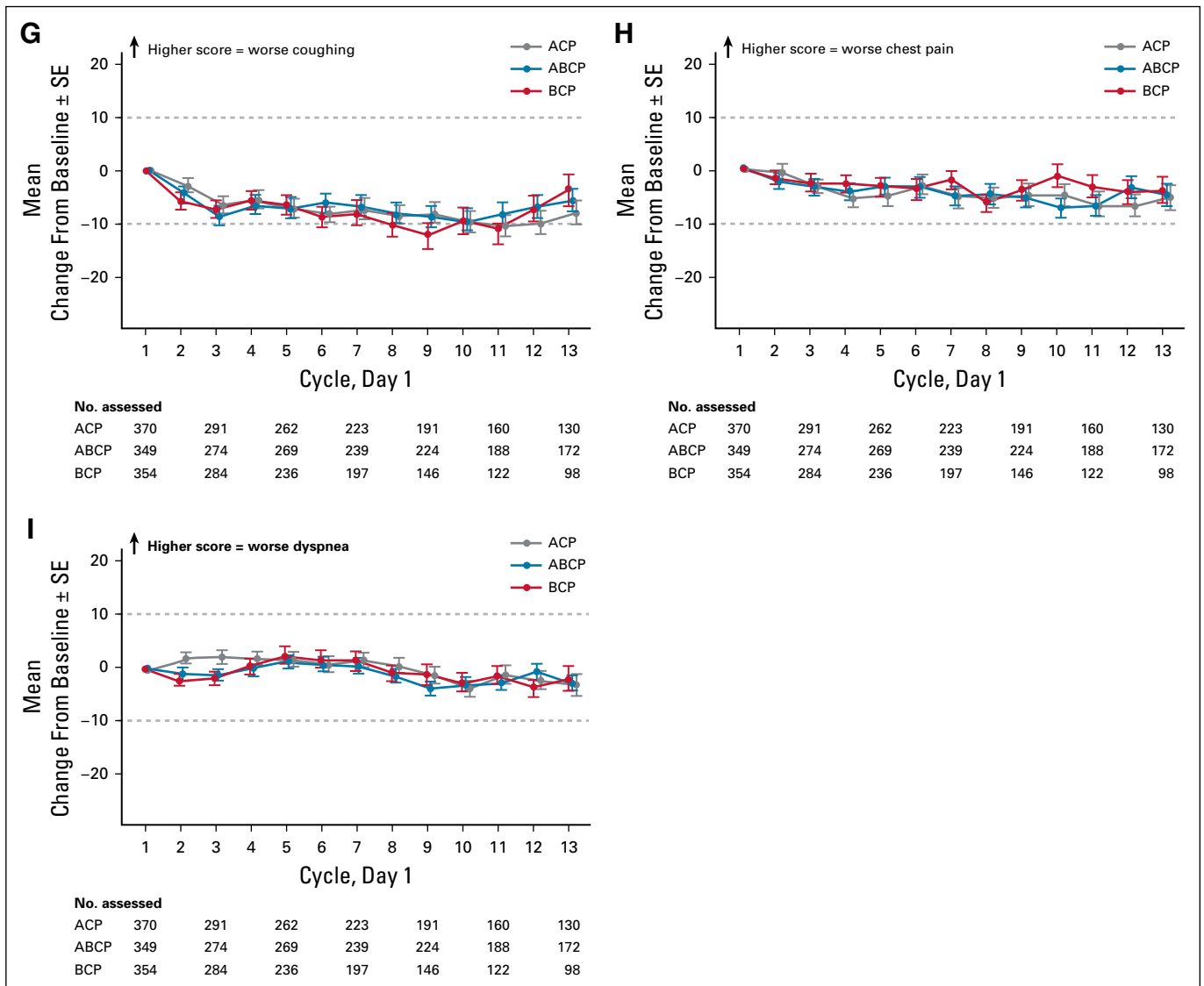


FIG 3. (Continued).

except for a lower incidence of hypothyroidism during the induction versus maintenance phase in both arms and a lower incidence of pneumonitis during the induction versus maintenance phase in the ACP arm. The time to onset and duration of the most common irAEs in the ACP and ABCP arms are shown in the Data Supplement. Most irAEs appeared within the first 3-4 months of treatment and persisted for approximately 2 months. Because systemic corticosteroids are often given to treat irAEs, corticosteroid use is also reported (Data Supplement).

PROs

Of the 400 patients in the ACP arm who received their intended treatment, 371 (92.8%) and 370 (92.5%), respectively, completed the EORTC QLQ-C30 and EORTC QLQ-LC13 at baseline. The respective rates of completion were 356 (90.6%) of 393 and 349 (88.8%) of 393 in the ABCP arm and 360 (91.4%) of 394 and 354 (89.8%) of

394 in the BCP arm. The completion rates documented in the intention-to-treat population were for patients who were active participants in the study at each time point, and they remained at $\geq 70\%$ completion through cycle 18 of treatment in all arms. PRO data were only interpreted up to cycle 13, at which point $\leq 25\%$ of patients in the BCP arm were still receiving treatment; in the intention-to-treat population, this limited the generalizability of the findings.

Patient-reported disease burden was comparable among treatment arms at baseline (cycle 1, day 1; Figs 2 and 3). Patients generally reported moderate to high functioning (higher scores indicate better HRQOL) and minimal symptom burden (lower scores indicate lower symptom severity) across arms (Data Supplement).

Patients on average did not report clinically meaningful worsening of global health status or physical functioning

scores at any point through cycle 13 in any treatment arm (Fig 2A). When analyzed by treatment phase, average global health status and physical functioning scores remained mostly similar during induction (Fig 2B), and physical functioning showed a trend toward improvement during maintenance (Fig 2C). Mean global health status and physical functioning scores were mostly similar in the ABCP and BCP arms across all time points analyzed.

Mean treatment-related symptom scores are shown in Figures 3A-3F; clinically meaningful worsening in peripheral neuropathy symptom severity was reported. Mean lung cancer–related symptom scores numerically improved in all treatment arms from baseline through cycle 13 (Figs 3G-3I), with a clinically meaningful improvement in coughing scores observed in the BCP arm at one or more treatment cycles.

DISCUSSION

No new safety signals were identified with ABCP, which thus confirms that the four-drug ABCP regimen had no additive toxicities compared with the three-drug ACP and BCP regimens in the phase III IMpower150 study.⁷ In addition, the improved PFS and OS observed with ABCP versus BCP⁷ was achieved while maintaining good HRQOL and physical functioning. Despite the higher grade 3/4 TRAE rates in the ABCP arm than in the ACP and BCP arms, these findings support the safety and tolerability of ABCP and provide insight on the ABCP regimen to the medical community beyond its regulatory approval.

Patients had longer exposure to study treatment with ABCP versus ACP or BCP. The AEs observed in the ABCP arm were mostly low grade and manageable, with numerically higher rates of treatment discontinuation compared with the BCP arm. The addition of atezolizumab to BCP did not lead to premature withdrawal from chemotherapy compared with BCP alone. Despite the addition of atezolizumab to the BCP regimen, the overall safety profile for atezolizumab in the combination remains similar to that of atezolizumab monotherapy.³

Across arms, patients reported no clinically meaningful worsening in mean HRQOL, physical functioning, or symptom scores at any point through cycle 13, except for patient-rated severity of peripheral neuropathy. PROs of treatment-related symptoms and safety particularly improved in the maintenance phase, a phenomenon that is well-known and not

surprising considering the discontinuation of chemotherapy. The PRO data suggest a minimal difference in treatment burden among arms and highlight an overall sense of the patient's well-being, which may not necessarily be reflected in the reporting of clinical safety, potentially because of the episodic nature of patient-reported symptoms. With the new options now available, including immunotherapy, future studies should explore approaches to reduce the burden of chemotherapy (eg, fewer cycles in subgroups that are more likely to benefit from immunotherapy) that might obscure the potential HRQOL advantages of immunotherapy.

Strengths of the PRO analyses conducted in this study include the large number of patients evaluated and the high rates of questionnaire completion across study arms through cycle 13. The EORTC QLQ-C30 and lung cancer–specific EORTC QLQ-LC13 are the most commonly used instruments for measuring HRQOL in patients with lung cancer and can be considered the standard option for HRQOL assessment in this population.³⁵ As a limitation, IMpower150 is an open-label trial, which could influence how patients perceived HRQOL. However, to date there is no evidence to indicate that receiving active treatments across the study arms would bias patients' assessments of symptom severity and impact on life.^{36,37} Furthermore, as a result of the reduction in the number of patients considered PRO evaluable over time, specifically in the BCP arm, PRO data were interpretable only up to cycle 13. The small patient numbers beyond this time point also limited longer-term PRO analyses. In addition, the EORTC QLQ-C30 and -LC13 were developed before the availability of cancer immunotherapy and, therefore, may miss certain symptoms (eg, rash) that could be experienced with such treatments. It should also be noted that IMpower150 has a select clinical trial population, with minimal symptoms that probably differ from those of real-life patients. Furthermore, this publication does not include a cost-effectiveness analysis, and as such, the value of this therapy given its reported clinical benefits, tolerability, and cost will need to be determined by stakeholders, including payers, health systems, clinicians, and patients. Overall, safety and PRO data from IMpower150 support the positive benefit-risk profile demonstrated by the clinical data with atezolizumab plus bevacizumab and chemotherapy in first-line nonsquamous NSCLC.

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DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: www.clinicalstudydatarequest.com. Additional details on Roche's criteria for eligible studies are available at <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, go to https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Safety and Patient-Reported Outcomes of Atezolizumab Plus Chemotherapy With or Without Bevacizumab Versus Bevacizumab Plus Chemotherapy in Non–Small-Cell Lung Cancer**

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