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ORIGINAL ARTICLE

Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial

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Background: The addition of atezolizumab to carboplatin and etoposide (CP/ET) significantly improved progression-free and overall survival for patients with extensive-stage small-cell lung cancer (ES-SCLC) in the IMpower133 study (NCT02763579). We have evaluated adverse events (AEs) and patient-reported outcomes in IMpower133 to assess the benefit—risk profile of this regimen.

Patients and methods: Patients received four 21-day cycles of CP/ET plus intravenous atezolizumab 1200 mg or placebo (induction phase), followed by atezolizumab or placebo (maintenance phase) until progression or loss of benefit. AEs were assessed and patient-reported outcomes were evaluated every 3 weeks during treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire — Core 30 (QLQ-C30) and QLQ-LC13.

Results: Overall, 394 patients were assessable for safety in the induction phase and 318 in the maintenance phase. The frequency of AEs, grade 3—4 AEs, and serious AEs was similar between arms in both phases. Immune-related AEs were more frequent in the atezolizumab arm during both induction (28% versus 17%; leading to atezolizumab/placebo interruption 9% versus 5%, leading to withdrawal 4% versus 0%) and maintenance (26% versus 15%; leading to atezolizumab/placebo interruption, 3% versus 2%, leading to withdrawal 1% versus 1%), most commonly rash (induction 11% versus 9%, maintenance 14% versus 4%), and hypothyroidism (induction 4.0% versus 0%, maintenance 10% versus 1%). Changes in patient-reported treatment-related symptoms commonly associated with quality of life impairment were generally similar during induction and most of the maintenance phase. Patient-reported function and health-related quality of life (HRQoL) improved in both arms after initiating treatment, with more pronounced and persistent HRQoL improvements in the atezolizumab arm.

Conclusions: In patients with ES-SCLC, atezolizumab plus CP/ET has a comparable safety profile to placebo plus CP/ET, and the addition of atezolizumab did not adversely impact patient-reported HRQoL. These data demonstrate the positive benefit—risk profile of first-line atezolizumab plus CP/ET in ES-SCLC and further support this regimen as a new standard of care in this setting.

Clinical trials number: NCT02763579.

Key words: atezolizumab, extensive-stage small-cell lung cancer, PD-L1, quality of life, safety, TECENTRIQ

INTRODUCTION

Until recently, standard first-line treatment of patients with extensive-stage small-cell lung cancer (ES-SCLC) was platinum and etoposide chemotherapy. Despite a median survival limited to approximately 10 months, there has been no significant improvement in overall survival (OS) in more than 20 years.[1,2] In the phase I/III IMpower133 trial (NCT02763579), the addition of the anti-programmed death-ligand 1 (PD-L1)

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antibody atezolizumab (Tecentriq®, F. Hoffmann-La Roche Ltd, Basel, Switzerland/Genentech, Inc., South San Francisco, CA) to carboplatin and etoposide (CP/ET) resulted in a significant improvement in OS, compared with placebo plus CP/ET [median 12.3 months versus 10.3 months, hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.54—0.91; $P = 0.007$]. Progression-free survival (PFS) was also significantly improved (median 5.2 months versus 4.3 months, HR 0.77; 95% CI 0.62—0.96; $P = 0.02$).[3] Atezolizumab plus CP/ET has been approved by the US Food and Drug Administration for first-line treatment of patients with ES-SCLC, representing a new standard of care in this setting.[4]

In assessing the overall benefit—risk profile of a new treatment regimen, particularly in a non-curative setting, it is important to consider the impact of disease and/or treatment burden on patients' safety and health-related quality of life (HRQoL), to ensure that the benefits of enhanced tumor control and increased survival do not come at the expense of increased toxicity and reduced HRQoL.[5,6]

Here we report the safety profile of atezolizumab combined with CP/ET in the induction and maintenance settings, and the impact of treatment on symptoms, functioning, and HRQoL from the patient's perspective, to inform overall treatment burden.

METHODS

Study design and patients

The design of the randomized, double-blind IMpower133 trial has been reported previously (supplementary Figure S1, available at *Annals of Oncology* online).[3] Briefly, patients with chemotherapy-naive ES-SCLC, stratified by sex (male versus female), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and presence of brain metastases (yes versus no) were randomly assigned 1 : 1 to receive four 21-day cycles of CP/ET with either intravenous (i.v.) atezolizumab 1200 mg or i.v. placebo on day 1 of each cycle (induction phase), followed by i.v. atezolizumab or placebo according to randomized assignment (maintenance phase), until unacceptable toxicity or disease progression; patients could continue treatment after progression per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 if there was evidence of clinical benefit. Prophylactic cranial irradiation (PCI) was permitted during the maintenance phase. The primary end points were OS and investigator-assessed PFS in the intention-to-treat population. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients provided written informed consent. An independent data and safety monitoring committee reviewed safety data regularly. Protocol approval was obtained from an independent ethics committee at each site.

Safety assessments

Patients were assessed for adverse events (AEs) before each dose, and dosing occurred only if the clinical assessment and local laboratory test values were acceptable. AEs were assessed according to National Cancer Institute — Common Terminology Criteria for Adverse Events version 4.0 and coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 terms. AEs of special interest (AESIs) were immune-related AEs defined based on the mechanism of action of atezolizumab, organized by medical concepts. AEs were recorded during the study, and for up to 30 days after the last dose of study treatment [90 days for serious AEs (SAEs) and AESIs], or until the initiation of new systemic anticancer therapy after the last dose of study treatment; whichever occurred first. After that period, any SAE or AESI was reported if it was considered related to prior exposure to study treatment by the investigators. Causality for AEs was assessed by the investigators. In an exploratory analysis, central nervous system (CNS)-related AEs were assessed in the subgroup of patients who received PCI.

Patient-reported outcome assessments

Patient-reported outcomes (PROs) were evaluated as secondary and exploratory end points and measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire — Core 30 (QLQ-C30) version 3[7] and the supplemental lung cancer

Table 1. Mean (SD) baseline EORTC QLQ-C30 and QLQ-LC13 scores

Baseline score, mean (SD)	Atezolizumab + CP/ET ($N = 201$)	Placebo + CP/ET ($N = 202$)
EORTC QLQ-C30 scales	$n = 179$	$n = 175$
Fatigue[a]	42.0 (26.4)	38.7 (26.9)
Appetite loss[a]	28.9 (32.3)	27.4 (31.9)
Constipation	22.7 (30.5)	22.7 (32.8)
Diarrhea	6.3 (15.7)	7.4 (17.9)
Dyspnea	41.9 (31.8)	36.4 (33.4)
Financial difficulties	24.8 (31.6)	22.9 (31.7)
Insomnia	37.6 (33.3)	34.1 (34.6)
Nausea/vomiting	9.6 (18.9)	10.5 (21.8)
Pain	33.6 (31.0)	31.9 (30.9)
Physical functioning	70.7 (22.7)	71.9 (23.5)
Role functioning	67.1 (31.3)	66.4 (32.9)
Social functioning	71.1 (29.1)	73.3 (28.8)
Emotional functioning	68.6 (23.9)	69.9 (24.0)
Cognitive functioning	81.8 (21.1)	83.3 (20.6)
Global health status	51.6 (22.4)	53.7 (23.4)
EORTC QLQ-LC13 scales	$n = 176$	$n = 168$
Cough[a]	42.2 (27.7)	42.9 (29.2)
Chest pain[a]	22.9 (26.6)	22.2 (25.7)
Dyspnea[a]	34.3 (25.9)	29.6 (25.9)
Arm/shoulder pain[a]	22.2 (30.6)	19.4 (27.4)
Alopecia	5.1 (16.9)	3.6 (15.1)
Dysphagia	11.2 (20.4)	10.1 (22.4)
Hemoptysis	5.3 (13.7)	8.5 (17.5)
Pain in other parts	24.1 (29.1)	27.4 (30.8)
Peripheral neuropathy	9.9 (20.3)	9.9 (21.8)
Sore mouth	5.5 (14.7)	8.9 (19.8)

Each scale score range is 0—100, where higher scores indicate better functioning or HRQoL in those scales and worse symptoms in the symptom scale.
CP/ET, carboplatin and etoposide; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Lung module; ES-SCLC, extensive-stage small-cell lung cancer; HRQoL, health-related quality of life; SD, standard deviation.
[a] (ES-)SCLC normative scores for the key disease-related symptoms of cough, chest pain, dyspnea, arm/shoulder pain, pain in other parts, fatigue, and appetite loss were 34.2, 16.0, 25.8, 12.7, 17.8, 43.5, and 31.5, respectively.

Table 2. Summary of safety in the induction and maintenance phases

Patients, *n* (%)	Induction phase		Maintenance phase	
	Atezolizumab + CP/ET (*n* = 198)	Placebo + CP/ET (*n* = 196)	Atezolizumab + CP/ET (*n* = 155)	Placebo + CP/ET (*n* = 163)
Patients with ≥1 AE	195 (98)	185 (94)	127 (82)	118 (72)
Grade 3–4 AEs	124 (63)	114 (58)	43 (28)	37 (23)
Grade 5 AEs	4 (2)	8 (4)	0 (0)	3 (2)
Serious AEs	57 (29)	53 (27)	24 (15)	19 (12)
AEs leading to discontinuation[a]				
Any treatment	13 (7)	3 (2)	8 (5)	2 (1)
Atezolizumab or placebo	10 (5)	2 (1)	8 (5)	2 (1)
CP or ET	1 (<1)	1 (<1)	—	—

AEs were analyzed by the phase (induction and maintenance) in which the AE onset occurred, although AEs starting in the induction phase could have continued into the maintenance phase of the study. Furthermore, AEs with onset in the maintenance phase may have been due to study treatment received in the induction phase.
AE, adverse event; CP/ET, carboplatin and etoposide.
[a] Excludes three patients in the atezolizumab + CP/ET arm and one patient in the placebo + CP/ET arm who withdrew due to an AE more than 21 days after the induction phase without having received any maintenance atezolizumab/placebo.

module, QLQ-LC13 (supplementary Methods, available at *Annals of Oncology* online).[8]

QLQ-C30 and QLQ-LC13 assessments were completed on day 1 of each 21-day treatment cycle at scheduled study visits during treatment, and at 3 months and 6 months after treatment discontinuation.

The PRO instruments, translated into the local language as required, were to be completed by patients on an electronic PRO device prior to administration of study treatment and prior to any other study assessments that might have biased their responses.

Statistical analysis

Full details regarding the statistical testing of this study have been described previously.[3] Safety and tolerability were assessed by clinical review of all relevant parameters, including AEs, vital signs, and laboratory values. Multiple occurrences of the same event in one individual were counted once at the highest grade.

PRO analyses were carried out in the intention-to-treat population without type I error control. Descriptive analyses included time to deterioration (TTD) and change from baseline summaries at each visit. Completion rates were calculated as the number of assessments received divided by the number of assessments expected at each visit among all randomized patients. TTD was defined as the time from randomization to a patient's first ≥10-point score change from baseline in a scale maintained for at least two consecutive PRO assessments, or followed by death within 3 weeks of the first ≥10-point score change. Stratified Cox regression models and Kaplan–Meier methods were used to estimate HRs and medians by treatment arm. For the group-level change from baseline summaries, a ≥10-point score change within an arm was considered clinically relevant.[9] Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patients and treatment

Between 6 June 2016 and 31 May 2017, 403 patients were randomized from 106 centers in 26 countries; 201 to the atezolizumab plus CP/ET arm and 202 to the placebo plus CP/ET arm (supplementary Figure S2, available at *Annals of Oncology* online) (clinical cut-off date was 24 April 2018).[3] The safety population was defined as patients who received a dose of any treatment and was grouped according to treatment received. There were 198 patients in the atezolizumab plus CP/ET safety arm and 196 in the placebo plus CP/ET safety arm. Patient-reported symptoms, functioning, and HRQoL scores were comparable between treatment arms at baseline (Table 1). Patients in IMpower133 generally reported worse disease-related symptoms (cough, chest pain, dyspnea, arm/shoulder pain, pain in other parts) at baseline compared with normative scores of patients with SCLC.[10]

Table 3. AEs commonly associated with quality of life impairment: incidence in the induction and maintenance phases

Patients, *n* (%)	Induction phase		Maintenance phase	
	Atezolizumab + CP/ET (*n* = 198)	Placebo + CP/ET (*n* = 196)	Atezolizumab + CP/ET (*n* = 155)	Placebo + CP/ET (*n* = 163)
Nausea	67 (34)	60 (31)	14 (9)	7 (4)
Vomiting	30 (15)	26 (13)	10 (6)	10 (6)
Constipation	42 (21)	51 (26)	12 (8)	9 (6)
Diarrhea	28 (14)	19 (10)	8 (5)	15 (9)
Decreased appetite	36 (18)	28 (14)	19 (12)	8 (5)
Dyspnea	15 (8)	13 (7)	6 (4)	6 (4)

AE, adverse event; CP/ET, carboplatin and etoposide.

Table 4. Incidence of immune-related AEs during the induction and maintenance phases

Patients, *n* (%)	Induction phase		Maintenance phase	
	Atezolizumab + CP/ET (*n* = 198)	Placebo + CP/ET (*n* = 196)	Atezolizumab + CP/ET (*n* = 155)	Placebo + CP/ET (*n* = 163)
Immune-related AEs (AESIs)				
Any	55 (28)	34 (17)	41 (26)	24 (15)
Leading to atezolizumab/placebo interruption	17 (9)	9 (5)	5 (3)	3 (2)
Leading to atezolizumab/placebo withdrawal	7 (4)	0 (0)	1 (1)	2 (1)
Immune-related AEs (any grade)				
Rash	21 (11)	17 (9)	21 (14)	6 (4)
Immune-related infusion-related reaction	11 (6)	10 (5)	0 (0)	1 (<1)
Immune-related hyperthyroidism	9 (5)	1 (<1)	2 (1)	4 (2)
Immune-related hypothyroidism	8 (4)	0 (0)	16 (10)	1 (<1)
Immune-related hepatitis (lab abnormalities)	8 (4)	6 (3)	8 (5)	3 (2)
Immune-related pneumonitis	3 (2)	0 (0)	1 (<1)	5 (3)
Immune-related colitis	3 (2)	0 (0)	0 (0)	0 (0)
Immune-related adrenal insufficiency	0 (0)	0 (0)	0 (0)	2 (1)
Immune-related pancreatitis	1 (<1)	1 (<1)	0 (0)	2 (1)
Immune-related nephritis	0 (0)	0 (0)	1 (<1)	1 (<1)
Myopathy/rhabdomyolysis	0 (0)	0 (0)	2 (1)	0 (0)
Immune-related severe cutaneous reaction	1 (<1)	0 (0)	2 (1)	0 (0)

Immune-related AEs reported in a single patient each were immune-related diabetes mellitus (atezolizumab arm) and immune-related vasculitis (placebo arm) during the induction phase, and immune-related Guillain—Barré syndrome and immune-related hypophysitis (both in the atezolizumab arm) during the maintenance phase.
AE, adverse event; AESI, adverse event of special interest; CP/ET, carboplatin and etoposide.

Safety

As previously reported,[3] exposure for all study treatment (atezolizumab/placebo, CP, and ET) was comparable between arms. Patients received a median of seven doses of atezolizumab and six of placebo. Median exposure to CP/ET was 2.2 months in each arm. The mean dose intensity of atezolizumab/placebo was 95% in both arms, while the mean dose intensity of CP/ET, respectively, was 92% and 89% in the atezolizumab arm and 93% and 90% in the placebo arm.[3] Most patients in both the atezolizumab plus CP/ET arm (80%) and the placebo plus CP/ET arm (90%) were able to complete the planned four cycles of induction treatment.

Atezolizumab plus CP/ET demonstrated an overall comparable safety profile to placebo plus CP/ET.[3]

This overall balanced safety profile was observed between the two arms over the course of treatment. The frequency of all-cause AEs, grade 3—4 AEs, and SAEs was similar between arms for both the induction and maintenance phases (Table 2). Discontinuation of any study treatment or of atezolizumab for AEs was higher in the atezolizumab plus CP/ET arm in the overall treatment course, with infusion-related reaction being the most common AE (≥2% incidence) for discontinuation of atezolizumab or any study treatment. There were fewer grade 5 AEs in the atezolizumab plus CP/ET arm, for both treatment phases (Table 2).

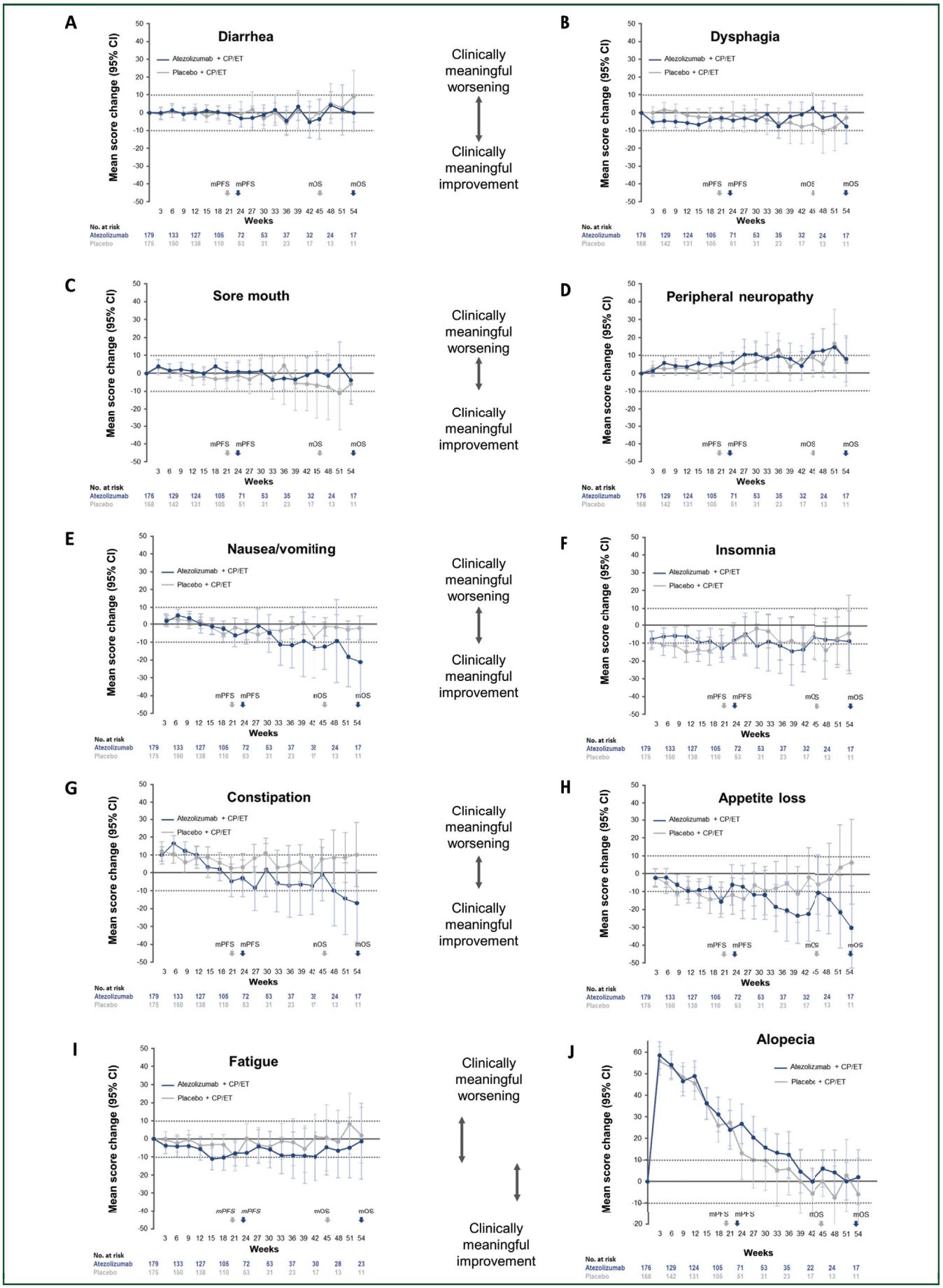
In the induction phase, the incidence of AEs commonly impacting patients' quality of life, such as nausea, vomiting, constipation, diarrhea, decreased appetite, and dyspnea, was similar between arms (Table 3). Notably, the incidence of such AEs was lower in the maintenance phase than in the induction phase, but was comparable between arms.

Immune-related AEs occurred in 40% of patients in the atezolizumab plus CP/ET arm and 24% of patients in the placebo plus CP/ET arm.[3] A higher incidence of immune-

Table 5. CNS-related AEs in all patients and in patients who received PCI

CNS-related AEs, *n* (%)	Atezolizumab + CP/ET			Placebo + CP/ET		
	All patients (*n* = 198)	Patients with PCI (*n* = 23)		All patients (*n* = 196)	Patients with PCI (*n* = 21)	
		AEs at any time	AEs after PCI[a]		AEs at any time	AEs after PCI[a]
Headache	24 (12)	8 (35)	6 (26)	23 (12)	3 (14)	3 (14)
Asthenia	25 (12)	5 (22)	1 (4)	20 (10)	2 (10)	0
Dizziness	19 (10)	2 (9)	0	11 (6)	0	0
Insomnia	15 (8)	3 (13)	1 (4)	13 (7)	1 (5)	1 (5)
Fall	8 (4)	2 (9)	1 (4)	4 (2)	1 (5)	1 (5)
Balance disorder	2 (1)	1 (4)	1 (4)	0	0	0
Lethargy	2 (1)	1 (4)	1 (4)	1 (<1)	0	0
Syncope	5 (3)	1 (4)	0	1 (<1)	0	0
Agitation	1 (<1)	0	0	1 (<1)	1 (5)	1 (5)
Confusional state	3 (2)	0	0	3 (2)	1 (5)	1 (5)

AE, adverse event; CP/ET, carboplatin and etoposide; CNS, central nervous system; PCI, prophylactic cranial irradiation.
[a] AEs with onset on or after day of PCI administration.


A
Diarrhea
B
Dysphagia
C
Sore mouth
D
Peripheral neuropathy
E
Nausea/vomiting
F
Insomnia
G
Constipation
H
Appetite loss
I
Fatigue
J
Alopecia
Atezolizumab + CP/ET
Placebo + CP/ET
Mean score change (95% CI)
Weeks
mPFS
mOS
No. at risk
Atezolizumab
Placebo
Clinically meaningful worsening
Clinically meaningful improvement

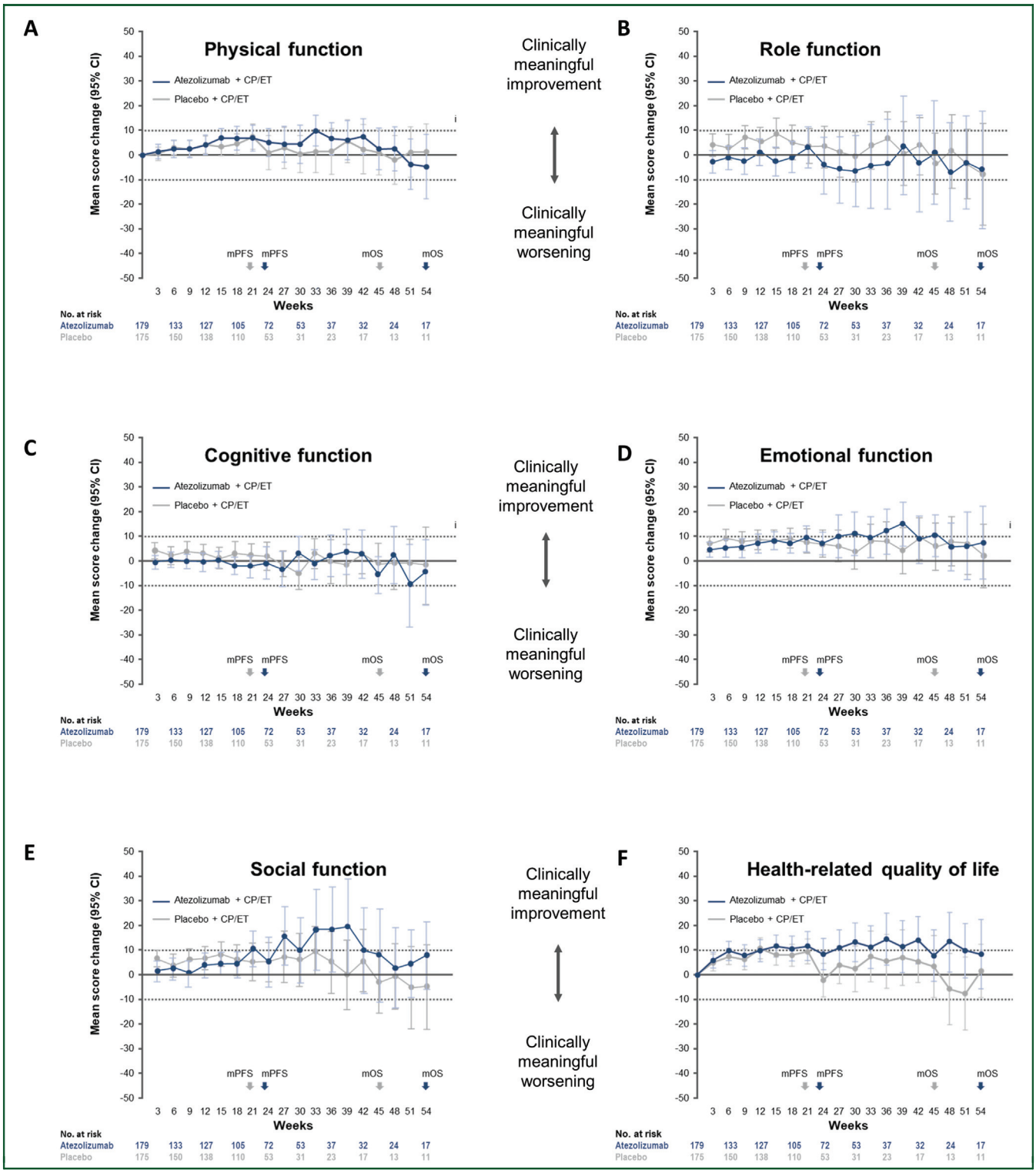


Figure 2. Changes from baseline through week 54 in function and health-related quality of life (HRQoL) in (A) physical function, (B) role function, (C) cognitive function, (D) emotional function, (E) social function, (F) HRQoL. Possible scores are 0−100 (i.e. maximum possible change is +100 to −100).
CI, confidence interval; CP, carboplatin; ET, etoposide; mOS, median overall survival; mPFS, median progression-free survival.

Figure 1. Changes from baseline through week 54 in treatment-related symptoms of (A) diarrhea, (B) dysphagia, (C) sore mouth, (D) peripheral neuropathy, (E) nausea/vomiting, (F) insomnia, (G) constipation, (H) appetite loss, (I) fatigue, (J) alopecia. Possible scores are 0−100 (i.e. maximum possible change is +100 to −100).
CI, confidence interval; CP, carboplatin; ET, etoposide; mOS, median overall survival; mPFS, median progression-free survival.

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related AEs, both overall and leading to atezolizumab/placebo interruption, was observed in the atezolizumab plus CP/ET arm for both treatment phases (Table 4).

Rash (both treatment arms) and hypothyroidism (atezolizumab plus CP/ET arm) were the most common (≥10% incidence) and most differentially reported (≥5% difference between arms) immune-related AEs during treatment overall. The rate of other immune-related AEs was similar between arms (<2% difference).

CNS-related AEs in patients who received PCI

In the subgroup of 44 patients who received PCI, a higher proportion of patients in the atezolizumab plus CP/ET arm experienced CNS-related AEs of headache, asthenia, and dizziness (Table 5).

PROs

At baseline, 175 patients in the atezolizumab plus CP/ET arm (87%) and 179 in the placebo plus CP/ET arm (89%) completed the QLQ-C30, and 176 (88%) and 168 (83%), respectively, completed the QLQ-LC13. Completion rates remained above 80% up to week 24 in the placebo arm and up to week 36 in the atezolizumab arm. For by-visit descriptive analyses, we focused on PRO data collected through week 54, which approximates median OS in the atezolizumab plus CP/ET arm. At week 54, 34 (8%) of the 403 randomized patients remained on study treatment and were eligible to complete PRO assessments.

Changes from baseline in treatment-related symptoms, including diarrhea, dysphagia, sore mouth, peripheral neuropathy, nausea/vomiting, and insomnia, were generally similar between arms at most visits through week 54 (Figure 1). Relative to baseline, trends of improvement in nausea/vomiting, fatigue, dysphagia, insomnia, and appetite loss were reported by patients in both arms. Patients in the placebo plus CP/ET arm reported greater improvements in constipation after week 12. Similar improvements in appetite loss were reported in both arms through week 33, after which improvements were more pronounced in the placebo plus CP/ET arm. Patients in the atezolizumab plus CP/ET arm reported improved fatigue above baseline maintained at all visits through week 54, while patients in the placebo plus CP/ET arm reported improved fatigue at most visits (13/18) through week 54. Patients in both arms experienced clinically meaningful worsening of alopecia after starting treatment that recovered to baseline approximately 9 months later.

An examination of PRO data collected through week 24 (approximately median PFS in the atezolizumab plus CP/ET arm) suggests generally consistent trends with PROs observed through week 54.

TTD of treatment-related symptoms, including peripheral neuropathy, sore mouth, alopecia, and dysphagia, were similar between arms (supplementary Figure S3, available at *Annals of Oncology* online). TTD of, and change from baseline in, lung cancer symptoms are shown in supplementary Figures S4 and S5, available at *Annals of Oncology* online.

In terms of the broader impacts of disease and treatment, early improvements in physical function were generally sustained in both arms at most visits through week 54 (Figure 2A). Similar trends in improvement or maintenance of pretreatment function (role, cognitive, emotional, social) were reported in the two arms through week 54 (Figure 2B—E). Patients in the atezolizumab plus CP/ET arm achieved meaningful improvements in HRQoL that persisted at most visits through week 54, whereas initial HRQoL improvements in the placebo plus CP/ET arm (mostly <10 points) tapered off after week 21 (Figure 2F).

DISCUSSION

This analysis assessed safety throughout the IMpower133 treatment phases and evaluated patient-reported symptoms, function, and HRQoL in the first-line ES-SCLC treatment setting. As previously reported, the combination of atezolizumab with CP/ET extended median survival from 10.3 months to 12.3 months (HR 0.7; 95% CI 0.54—0.91; $P = 0.007$) and improved the 1-year survival rate from 38.2% to 51.7%.[3] Additionally, the overall safety profile of atezolizumab plus CP/ET was comparable to placebo plus CP/ET, with no new safety findings.[3] In this non-curative setting, it is important that the extra period of life achieved with the addition of atezolizumab to standard chemotherapy does not come at the cost of impaired quality of life.

PROs were, overall, consistent with safety findings, though no direct comparisons or linkages were made. In general, no notable differences in treatment-related symptoms (e.g. diarrhea, sore mouth) were observed between arms at induction visits, at the end of induction, and at most visits through week 54. Positive trends of improvement in some symptoms (e.g. nausea/vomiting, fatigue, insomnia, appetite loss) were reported by patients in both arms. Time to meaningful worsening of treatment-related symptoms (e.g. peripheral neuropathy, alopecia) was also similar between arms. Notably, there were few deterioration events in each arm.

Considering the broader impact of symptoms on patients' global health status, while HRQoL improved in both arms, clinically meaningful improvements persisted in the atezolizumab plus CP/ET arm through week 54, suggesting that the survival benefit achieved with the addition of atezolizumab to CP/ET was associated with minimal impact on treatment-related symptoms. Taken together, the notable HRQoL improvements reported by patients in the atezolizumab arm suggest that the addition of atezolizumab to CP/ET did not increase toxicity or symptom burden.

Strengths of this study include the high-quality, complete PRO data collected in both treatment arms throughout the study in a blinded fashion. These analyses of nearly 400 patients add to the limited experience with immune checkpoint inhibitors and an established chemotherapy regimen in ES-SCLC regarding safety and patient-relevant impacts. Nevertheless, the relatively small number of patients eligible for PRO assessments in the later treatment cycles of the study may limit the ability to draw definitive conclusions;

accordingly, we summarized descriptively the numerical trends over the course of treatment within each treatment arm through week 54.

In conclusion, these analyses show that addition of atezolizumab to standard chemotherapy, which improves both OS and PFS in IMpower133[3] with comparable safety, does not significantly increase overall treatment burden. Overall, efficacy, safety, and PRO data from IMpower133 demonstrate the positive benefit—risk profile of first-line atezolizumab plus CP/ET in ES-SCLC and further support this regimen as a new standard of care.

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DATA-SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: www.clinicalstudydatarequest.com. Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: 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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