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Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer

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ABSTRACT

Purpose
Patients with extensive-stage disease small-cell lung cancer (SCLC) have poor survival outcomes despite first-line chemotherapy with etoposide and platinum. This randomized, double-blind phase III study evaluated the efficacy and safety of ipilimumab or placebo plus etoposide and platinum in patients with newly diagnosed extensive-stage disease SCLC.

Patients and Methods
Patients were randomly assigned at a ratio of one to one to receive chemotherapy with etoposide and platinum (cisplatin or carboplatin) plus ipilimumab 10 mg/kg or placebo every 3 weeks for a total of four doses each in a phased induction schedule (chemotherapy in cycles one to four; ipilimumab or placebo beginning in cycle three up to cycle six), followed by ipilimumab or placebo maintenance every 12 weeks. Primary end point was overall survival (OS) among patients receiving at least one dose of blinded study therapy.

Results
Of 1,132 patients randomly assigned, 954 received at least one dose of study therapy (chemotherapy plus ipilimumab, n = 478; chemotherapy plus placebo, n = 476). Median OS was 11.0 months for chemotherapy plus ipilimumab versus 10.9 months for chemotherapy plus placebo (hazard ratio, 0.94; 95% CI, 0.81 to 1.09; P = .3775). Median progression-free survival was 4.6 months for chemotherapy plus ipilimumab versus 4.4 months for chemotherapy plus placebo (hazard ratio, 0.85; 95% CI, 0.75 to 0.97). Rates and severity of treatment-related adverse events were similar between arms, except for diarrhea, rash, and colitis, which were more frequent with chemotherapy plus ipilimumab. Rate of treatment-related discontinuation was higher with chemotherapy plus ipilimumab (18% *v* 2% with chemotherapy plus placebo). Five treatment-related deaths occurred with chemotherapy plus ipilimumab and two with chemotherapy plus placebo.

Conclusion
Addition of ipilimumab to chemotherapy did not prolong OS versus chemotherapy alone in patients with newly diagnosed extensive-stage disease SCLC. No new or unexpected adverse events were observed with chemotherapy plus ipilimumab. Several ongoing studies are evaluating ipilimumab in combination with programmed death-1 inhibitors in SCLC.

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INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for 10% to 15% of lung cancer cases,[1] is an extremely aggressive tumor type; 70% of patients present with extensive-stage disease (ED-SCLC).[2,3] The current first-line standard of care is platinum-based chemotherapy (four to six cycles of etoposide plus either cisplatin or carboplatin) in the United States and Europe[4-7] and irinotecan plus a platinum agent in Japan.[8] Despite high initial response rates, nearly all patients with ED-SCLC experience disease recurrence or rapid progression after first-line chemotherapy. The median progression-free survival [PFS] is approximately 2 to 3 months,[9] and long-term survival remains poor (2-year overall survival [OS] is < 5%).[3,10] Multiple trials evaluating other

agents or the addition of a third drug have failed to show a significant improvement in median OS over etoposide and platinum.[3,10,11] Thus, there is a significant need for effective therapy.

Several lines of evidence provide a rationale for the use of immunotherapy in SCLC. The high frequency of somatic mutations in SCLC,[3,12] along with the presence of autoimmune paraneoplastic syndromes,[13,14] suggests that SCLC is an immunogenic tumor type. Preliminary studies have shown activity of immune checkpoint inhibitors in SCLC.[15-17]

Ipilimumab, a fully human immunoglobulin G1 monoclonal antibody that abrogates binding of the checkpoint protein cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) with its ligands, significantly improved OS in patients with advanced melanoma in two phase III trials.[18-20] Ipilimumab has also been evaluated in combination with chemotherapy in preclinical and clinical studies of different tumor types.[17,19,21-23] In a phase II trial, ipilimumab administered in a phased regimen with carboplatin and paclitaxel significantly improved immune-related PFS over carboplatin and paclitaxel alone and showed a numeric though not statistically significant increase in median OS over carboplatin and paclitaxel (12.9 *v* 9.9 months) in patients with previously untreated ED-SCLC.[17] The phased ipilimumab regimen also significantly improved immune-related PFS and PFS over carboplatin and paclitaxel alone in patients with previously untreated non-SCLC (NSCLC).[23] The phase II results[17] and preclinical data[22] led to the initiation of this multicenter, randomized, double-blind phase III trial evaluating ipilimumab or placebo in combination with etoposide and platinum therapy in patients with newly diagnosed ED-SCLC (CA184-156 study [clinical trial information: NCT01450761]).

PATIENTS AND METHODS

Patients

Patients with documented ED-SCLC were eligible. Inclusion criteria included age 18 years or older, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and no prior systemic therapy for ED-SCLC. Exclusion criteria included brain metastasis requiring treatment, uncontrolled pleural effusion, autoimmune disease, systemic immunosuppression, and any cancer immunotherapy.

The study protocol was approved by the institutional review board or ethics committee at each participating center as appropriate and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent before enrollment. An independent data and safety monitoring committee provided oversight of safety and efficacy.

Study Design and Treatment Plan

The study consisted of induction followed by a maintenance phase (Data Supplement). Patients were randomly assigned at a ratio of one to one to receive ipilimumab 10 mg/kg intravenously (IV) or placebo using an interactive voice response system with a stratified, permuted, block-randomization method. Research staff was blinded to treatment assignment. Ipilimumab or placebo was administered in a phased dosing regimen. During cycles one to four of induction (3-week cycles), patients in both arms received etoposide 100 mg/m^2 IV on days 1, 2, and 3 of each cycle and investigator's choice of platinum agent on day 1 of each cycle (cisplatin 75 mg/m^2 IV or carboplatin area under the concentration-time curve 5 IV). During cycles three and four of induction, patients received ipilimumab 10 mg/kg or placebo (3-week cycles) in addition to chemotherapy; during cycles five and six of induction, patients received only ipilimumab or placebo (Data Supplement). Patients who achieved a complete or partial response per modified WHO criteria[24] during induction could undergo prophylactic cranial irradiation (PCI; investigator's choice) before the start of the maintenance phase. The maintenance phase began 9 to 12 weeks after the last induction cycle (depending on the timing of and recovery from PCI, if administered). Ipilimumab 10 mg/kg or placebo was administered every 12 weeks until progression, unacceptable toxicity, or death, for a maximum of 3 years from the first ipilimumab or placebo dose. The rationale for this dose schedule of ipilimumab was based on prior phase II/III melanoma and phase II lung cancer trials.[17,19,23,25-27]

Random assignment was stratified by ECOG PS (0 *v* 1), lactate dehydrogenase level ($\leq$ upper limit of normal *v* $>$ upper limit of normal), choice of platinum agent during induction (cisplatin *v* carboplatin), and region (North America or Western Europe *v* other). Criteria for treatment delay and discontinuation because of treatment-related adverse events (AEs) are detailed in the Data Supplement. No dose reductions were permitted for ipilimumab or placebo. Results are provided for patients who were treated with at least one dose of blinded study drug.

Treatment Assessments

Tumor assessment (including bone or brain imaging) performed at screening was used as baseline for efficacy assessments. Tumor response was investigator assessed per modified WHO criteria at weeks 7, 13, 19, and 25 and then every 12 weeks thereafter until progression or end of treatment. Safety was assessed by evaluating the incidence of AEs and laboratory parameters and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). AEs of interest were defined as those with potential immunologic etiologies and grouped into predefined categories: enterocolitis, dermatitis, hepatitis, endocrinopathies, and neuropathies. AEs of interest considered drug related by the investigator were referred to as immune-related AEs.

End Points

The primary end point was OS among patients who received at least one dose of study therapy. Patients were observed continuously for survival while receiving treatment and then every 3 months after treatment discontinuation.

The trial was originally designed with a primary end point of OS in all randomly assigned patients. During the study, it was determined that the effect of ipilimumab on OS could not be accurately measured in this population of all those randomly assigned. To avoid attenuation of the potential treatment effect, the end points were modified by a protocol amendment.

Secondary end points included OS in all randomly assigned patients and PFS per modified WHO criteria among patients who received at least one dose of study therapy. Exploratory end points included best overall response rate (ORR), duration of response, survival rate, and safety.

Statistical Analyses

Estimation of sample size was based on the results of a phase II study in ED-SCLC and NSCLC.[17,23] Approximately 1,100 patients were to be randomly assigned at a ratio of one to one; assuming a dropout rate of 15% during the first two cycles of chemotherapy, it was estimated 935 patients would receive study drug. The primary analysis was not conducted until a total of 618 events had occurred in 935 randomly assigned patients who received study therapy, which was estimated to ensure 90% power to detect a statistically significant difference in OS, with a type I error rate of 5% based on a two-sided log-rank test. For this power computation, an exponential distribution and a true hazard ratio (HR) of 0.77 in the post-chemotherapy alone period was assumed. The expected smallest statistically significant treatment effect corresponded to an HR of 0.85.

For OS and PFS, treatment arms were compared using an unstratified, two-sided log-rank test. HRs and corresponding 95% CIs were estimated using an unstratified Cox model with treatment arm as the only

covariate. Survival curves and rates were estimated using the Kaplan-Meier method. Best ORR per modified WHO criteria was calculated in evaluable patients, and corresponding 95% exact CI was calculated using the Clopper-Pearson method. Statistical considerations in all randomly assigned patients are presented in the Data Supplement.

RESULTS

Patients and Treatment

From January 2012 to September 2014, 1,414 patients were enrolled at 224 study sites in 34 countries, with 1,132 patients randomly assigned to receive etoposide and platinum plus ipilimumab (chemotherapy plus ipilimumab) or etoposide and platinum plus placebo (chemotherapy plus placebo; n = 566 in each arm). A total of 1,123 patients received treatment (one or more cycle of platinum and etoposide); the most common reason for not receiving treatment was that the patient no longer met eligibility criteria. Of those treated, 15% of patients (n = 169) discontinued during cycles one to two, before administration of study drug, and 85% (n = 954) received at least one dose of blinded study therapy (chemotherapy plus ipilimumab, [n = 478]; chemotherapy plus placebo, [n = 476]; Fig 1; Data Supplement). This report focuses on efficacy and safety analyses performed in randomly assigned patients who received at least one dose of blinded study drug. Analyses in the population of all those randomly assigned are presented in the Data Supplement.

Median age of the treated patient population was 62 years; most patients were male (67%) and white (76%), with an ECOG

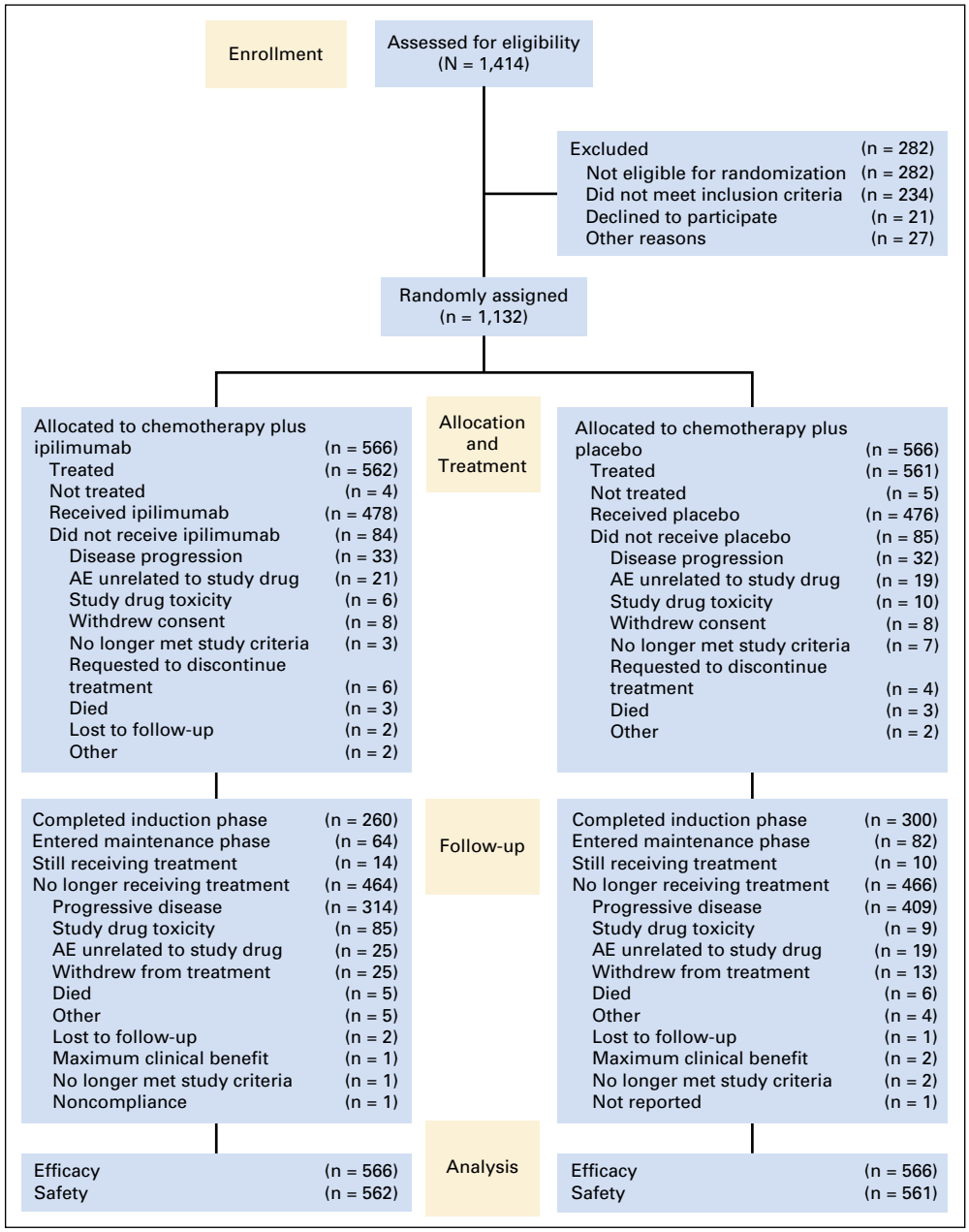

Fig 1. CONSORT diagram. Disposition of patients with extensive-stage small-cell lung cancer in study CA184-156 as of September 2015. Patients were randomly assigned to chemotherapy plus ipilimumab (etoposide plus investigator's choice of cisplatin or carboplatin in cycles one to four and ipilimumab in cycles three to six) or chemotherapy plus placebo (etoposide plus investigator's choice of cisplatin or carboplatin in cycles one to four and placebo in cycles three to six). Patients who achieved complete or partial response per modified WHO criteria[24] during induction could undergo prophylactic cranial irradiation (PCI), investigator's choice, before start of maintenance phase. Maintenance phase began 9 to 12 weeks after last induction cycle (depending on timing of and recovery from PCI, if administered), in which ipilimumab 10 mg/kg or placebo was administered intravenously every 12 weeks until progression, unacceptable toxicity, or death, for a maximum period of 3 years from first ipilimumab or placebo dose. Reasons for patients discontinuing during induction phase are indicated. AE, adverse event.

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PS of 1 (70%). Demographic and baseline characteristics were balanced between the two arms (Table 1).

The median number of doses of blinded study drug received was four (ipilimumab, range one to 14; placebo, range one to 12); 59% received at least four doses of ipilimumab, and 69% received at least four doses of placebo. The number of patients who received carboplatin or cisplatin as backbone chemotherapy was similar between treatment arms (Data Supplement). Across arms, 15% of patients (n = 146) received at least one dose of maintenance therapy (ipilimumab, 13% [n = 64]; placebo, 17% [n = 82]; Fig 1). At database lock (June 10, 2015), 3% of patients (n = 24) continued in the maintenance phase (chemotherapy plus ipilimumab, [n = 14]; chemotherapy plus placebo, [n = 10]); the most common reason for discontinuation was disease progression (Fig 1; Data Supplement). PCI was administered to 11% and 14% of patients in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively. Subsequent chemotherapy was administered to 48% and 52% of patients in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively (Data Supplement).

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy

Characteristic	No. (%) Chemotherapy Plus Ipilimumab (n = 478)	No. (%) Chemotherapy Plus Placebo (n = 476)
Age, years		
Median	62	63
Range	39 to 85	36 to 81
Age categorization, years		
< 65	299 (63)	277 (58)
≥ 65	179 (37)	199 (42)
Sex		
Male	317 (66)	326 (68)
Female	161 (34)	150 (32)
Race		
White	365 (76)	359 (75)
Asian	108 (23)	107 (22)
Black/African American	3 (1)	5 (1)
Other	2 (< 1)	5 (1)
Region		
North America or Western Europe	186 (39)	197 (41)
Rest of world*	292 (61)	279 (59)
ECOG PS		
0	137 (29)	147 (31)
1	340 (71)	328 (69)
2	1 (< 1)	1 (< 1)
CNS metastasis at baseline	55 (12)	45 (10)
Smoking status		
Heavy smoker†	268 (56)	271 (57)
Light or nonsmoker‡	172 (36)	167 (35)
Unknown	9 (2)	11 (2)
Missing	29 (6)	27 (6)
LDH level		
> ULN	231 (48)	228 (48)
≤ ULN	242 (51)	246 (52)
Not reported	2 (< 1)	2 (< 1)
Choice of platinum during induction		
Cisplatin	164 (34)	159 (33)
Carboplatin	314 (66)	317 (67)
Patients with prior surgery	65 (14)	72 (15)
Patients with prior radiotherapy	14 (3)	8 (2)
Time from initial diagnosis to first dose, months		
Median	0.6	0.5
Range	0 to 109.2	0 to 1,081.6

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.
*Includes countries in Africa, Asia, Australia, Eastern Europe, and South America.
†Defined as > 20 pack-years and currently smoking or stopped < 1 year ago.
‡All patients who did not meet criteria for heavy smoker.

Efficacy

At database lock, 74% of patients (n = 707) who received blinded study therapy had died. Median follow-up for OS was 10.5 and 10.2 months in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively.

Chemotherapy plus ipilimumab treatment did not result in a statistically significant improvement in OS compared with chemotherapy plus placebo among patients who received at least one dose of blinded study therapy (HR, 0.94; 95% CI, 0.81 to 1.09; unstratified log-rank P = .3775). Median OS was 11.0 months (95% CI, 10.45 to 11.33) in patients treated with chemotherapy plus ipilimumab versus 10.9 months (95% CI, 10.02 to 11.50) in those treated with chemotherapy plus placebo, with 1-year OS rates of 40% in both arms (Fig 2A). At the time of analysis, 350 patients (73%) in the chemotherapy plus ipilimumab arm had died, compared with 357 (75%) in the chemotherapy plus placebo arm. Across most prespecified patient subgroups, HRs for OS did not seem to favor one treatment arm (Fig 2B). Results for OS in the population of all randomly assigned patients were consistent with the primary analysis results (Data Supplement).

Median PFS was 4.6 months (95% CI, 4.50 to 4.99) in patients treated with chemotherapy plus ipilimumab versus 4.4 months (95% CI, 4.37 to 4.63) in those treated with chemotherapy plus placebo; HR was 0.85 (95% CI, 0.75 to 0.97; unstratified log-rank P = .0161) between arms (Fig 3). At the time of analysis, 443 (93%) and 457 patients (96%) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively, had experienced disease progression. Furthermore, because the primary end point of the study was not met, the P values of all secondary end points, including PFS, are provided for descriptive purposes only and should not be considered statistically significant.

Best ORRs were similar in the two arms. In the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively, 62% (in each arm) experienced partial responses, 26% and 27% experienced stable disease, and 6% and 9% experienced progressive disease. One patient treated with chemotherapy plus ipilimumab experienced a complete response; none were observed in patients treated with chemotherapy plus placebo. Median duration of response was 4.01 (95% CI, 3.32 to 4.17) and 3.45 months (95% CI, 3.25 to 4.07) with chemotherapy plus ipilimumab and chemotherapy plus placebo, respectively (Table 2).

Safety

Rate of treatment-related AEs occurring on or after blinded study drug dosing was 82% (48% for grade 3 to 4 events) with chemotherapy plus ipilimumab and 76% (44% for grade 3 to 4 events) with chemotherapy plus placebo (Table 3). The most

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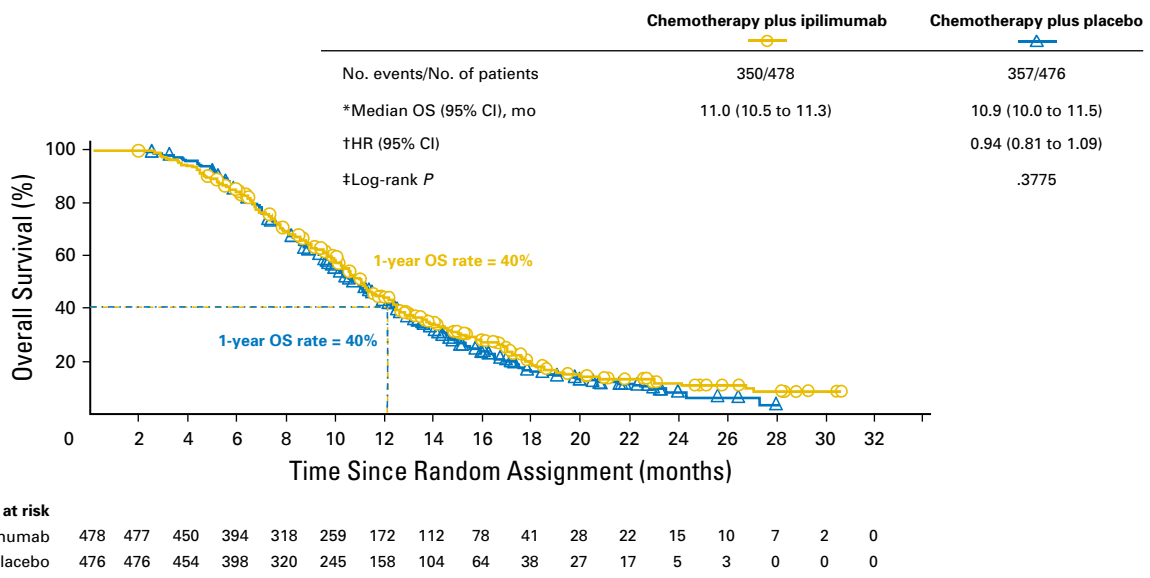

No. of patients at risk

Chemotherapy plus ipilimumab	478	477	450	394	318	259	172	112	78	41	28	22	15	10	7	2	0
Chemotherapy plus placebo	476	476	454	398	320	245	158	104	64	38	27	17	5	3	0	0	0

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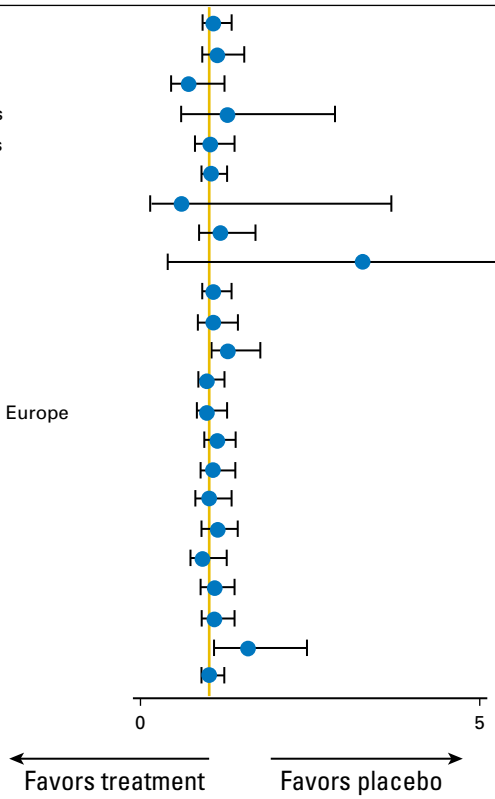

	Ipilimumab No. of events (No. of patients)	Placebo No. of events (No. of patients)	HR (95% CI)
Age < 65 years	224 (299)	211 (277)	1.08 (0.90 to 1.31)
Age ≥ 65 to < 75 years	100 (147)	118 (159)	1.14 (0.87 to 1.49)
Age ≥ 75 years	26 (32)	28 (40)	0.70 (0.40 to 1.20)
Female and age < 50 years	15 (22)	10 (12)	1.26 (0.56 to 2.85)
Female and age ≥ 50 years	102 (139)	101 (138)	1.04 (0.79 to 1.39)
White	280 (365)	284 (359)	1.05 (0.89 to 1.24)
Black	2 (3)	3 (5)	0.60 (0.10 to 3.68)
Asian	66 (108)	65 (107)	1.16 (0.82 to 1.64)
Other race	2 (2)	5 (5)	3.32 (0.38 to 28.94)
Male	233 (317)	246 (326)	1.07 (0.89 to 1.28)
Female	117 (161)	111 (150)	1.06 (0.81 to 1.37)
Baseline ECOG PS of 0	94 (137)	116 (147)	1.28 (0.98 to 1.69)
Baseline ECOG PS of 1	255 (340)	240 (328)	0.99 (0.83 to 1.18)
North America or Western Europe	149 (183)	156 (194)	1.00 (0.80 to 1.25)
Other region	201 (295)	201 (282)	1.11 (0.91 to 1.35)
Heavy smoker	194 (268)	204 (271)	1.09 (0.89 to 1.32)
Ex-, light, or nonsmoker	130 (172)	126 (167)	1.02 (0.80 to 1.30)
Carboplatin	238 (314)	250 (317)	1.14 (0.96 to 1.37)
Cisplatin	112 (164)	107 (159)	0.93 (0.71 to 1.21)
Baseline LDH elevated	186 (231)	187 (228)	1.10 (0.90 to 1.35)
Baseline LDH within ULN	163 (245)	169 (246)	1.08 (0.87 to 1.34)
CNS metastasis	41 (55)	41 (45)	1.58 (1.02 to 2.44)
No CNS metastasis	309 (423)	316 (431)	1.03 (0.88 to 1.20)

Fig 2. (A) Overall survival (OS) and (B) treatment effect on OS in predefined subsets. (A) Kaplan-Meier plot of OS (chemotherapy plus ipilimumab, [n = 478]; chemotherapy plus placebo, [n = 476]). OS was defined as time from date of random assignment until date of death. As indicated by symbols, patients who had not died or were lost to follow-up were censored on the last date they were known to be alive. Horizontal lines indicate rates of OS at 1 year. (B) Forest plot of treatment effect on OS in predefined subsets based on unstratified Cox proportional hazards model for patients in indicated subset. Hazard ratios (HRs) and two-sided 95% CIs were calculated as in panel A. ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal. (*) Medians and associated two-sided CIs calculated via log-log transformation. (†) Hazard of ipilimumab over hazard of placebo with two-sided 95% CI is based on unstratified Cox proportional hazards model with treatment as single covariate. (‡) Unstratified two-sided log-rank test.

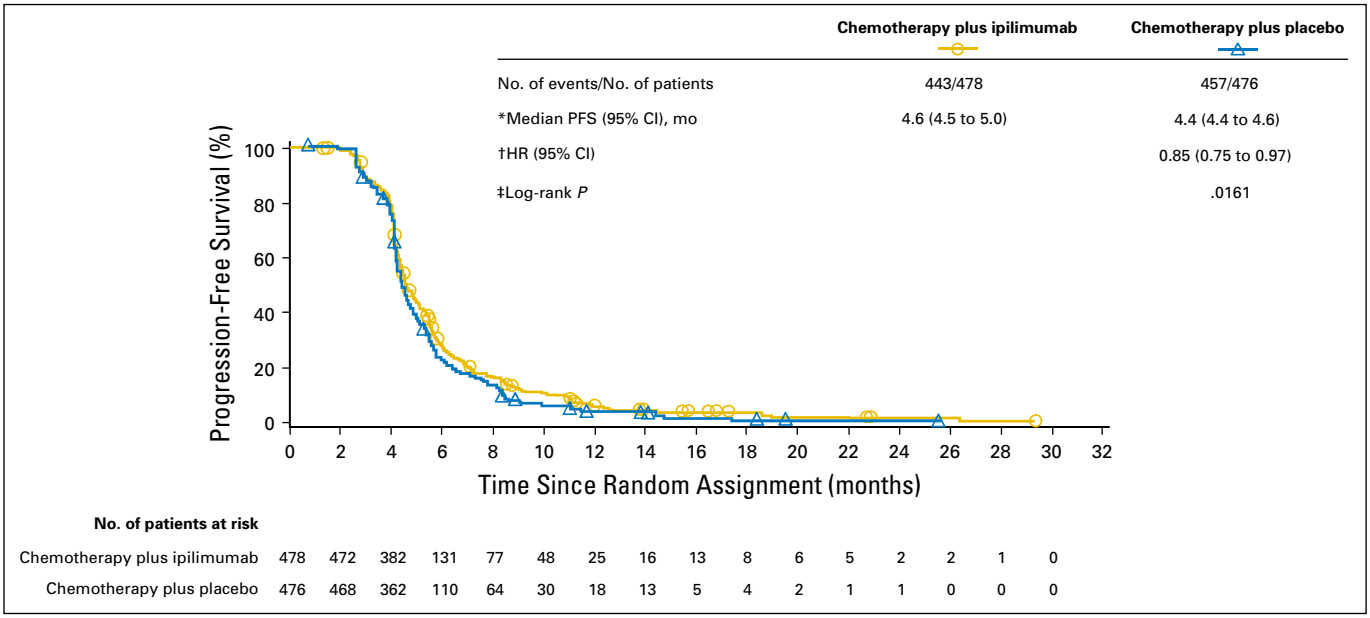

Fig 3. Kaplan-Meier plot of progression-free survival (PFS). Chemotherapy plus ipilimumab, (n = 478); chemotherapy plus placebo, (n = 476). Per modified WHO criteria,[24] increase in target lesions of ≥ 25% from baseline, progression of nonindex lesions, or presence of new lesion (measurable or not) is considered progression. PFS per modified WHO criteria was defined as the time between date of random assignment and date of progression per modified WHO criteria or death, whichever occurred first. As indicated by symbols, patients who were alive and did not experience progression were censored on the date of last evaluable tumor assessment. HR, hazard ratio. (*) Medians and associated two-sided CIs calculated via log-log transformation. (†) Hazard of ipilimumab over hazard of placebo with two-sided 95% CI based on unstratified Cox proportional hazards model with treatment as the single covariate. (‡) Unstratified two-sided log-rank test.

frequently reported grade 3 to 4 treatment-related AEs occurring in 5% of patients or more in the chemotherapy plus ipilimumab arm were neutropenia (14%), anemia (8%), diarrhea (7%), and decreased neutrophil count (7%). In the chemotherapy plus placebo arm, they were neutropenia (24%), anemia (11%), and decreased neutrophil count (6%). Frequency of treatment-related serious AEs was numerically higher with chemotherapy plus ipilimumab (any grade, 27%; grade 3 to 5, 22%) versus chemotherapy plus placebo (any grade, 13%; grade 3 to 5, 11%; Data Supplement). A majority of treatment-related serious AEs occurred in less than 1% of patients; incidence was similar between arms, with the exception of diarrhea (any grade, 8% *v* 1%) and colitis (any grade, 5% *v* < 1%), which occurred more frequently with chemotherapy plus ipilimumab (Data Supplement).

Treatment-related AEs led to discontinuation in 18% of patients treated with chemotherapy plus ipilimumab and 2% of those treated with chemotherapy plus placebo (Data Supplement). The most frequent treatment-related AEs leading to discontinuation were diarrhea (5%) and colitis (4%) with chemotherapy plus ipilimumab. In the chemotherapy plus ipilimumab arm, there were five treatment-related deaths, two resulting from colitis, two from sepsis, and one from liver toxicity. The two deaths resulting from sepsis were assessed by investigators as being related to chemotherapy but not ipilimumab. In the chemotherapy plus placebo arm, there were two treatment-related deaths, one resulting from sepsis and one from bone marrow suppression (Data Supplement).

GI and skin-related AEs were the most common immune-related AEs with chemotherapy plus ipilimumab (in 34% and 29% of patients, respectively). The most frequently reported immune-related AEs in 5% or more of patients treated with chemotherapy plus ipilimumab versus chemotherapy plus placebo were diarrhea (25% *v* 10%), rash (19% *v* 3%), pruritus (12% *v* 2%), colitis (6% *v* < 1%), and alopecia (5% *v* 7%). Endocrine immune-related AEs occurred in 10% of patients in the chemotherapy plus ipilimumab arm versus 2% in the chemotherapy plus placebo arm; the most frequently reported events in 1% or more of patients were hypothyroidism (3%), hyperthyroidism (2%), hypophysitis (1%), and adrenal insufficiency (1%), as shown in the Data Supplement.

In the chemotherapy plus ipilimumab arm, median times to onset of grade 2 to 5 immune-related AEs ranged from 4.7 weeks in the skin category to 9.0 weeks in the hepatic category (Data Supplement). Immune-related AEs were managed using established safety guidelines. At database lock, a majority (76%; 184 of 243) of grade 2 to 4 immune-related AEs completely resolved, with median times to resolution ranging from 2.0 weeks for hepatic events to 28.9 weeks for neurologic events (Data Supplement).

DISCUSSION

To our knowledge, study CA184-156 is the largest phase III randomized trial conducted to date in a population of patients with ED-SCLC. The addition of ipilimumab to etoposide and platinum did not result in a statistically significant improvement in OS versus etoposide and platinum. Although exploratory in nature, chemotherapy plus ipilimumab did not demonstrate significant improvement in other end points, and no subgroups demonstrated greater benefit versus chemotherapy alone. Baseline characteristics were well balanced between arms; treatment delivery was comparable, and the frequency and reasons for patients discontinuing during cycles one and two (before start of blinded study drug) and in patients who went on to receive at least one dose of blinded study drug were consistent with prior observations.[17,23] Post-study

Table 2. Tumor Response

Best Overall Response	No. (%)	
	Chemotherapy Plus Ipilimumab (n = 478)	Chemotherapy Plus Placebo (n = 476)
Best overall response rate*	297 (62)	296 (62)
95% CI	58 to 67	58 to 67
Complete response	1 (< 1)	0
Partial response	296 (62)	296 (62)
Stable disease	125 (26)	126 (27)
Progressive disease	29 (6)	42 (9)
Unknown	27 (6)	12 (3)
Duration of response, months†		
Median	4.01	3.45
95% CI	3.32 to 4.17	3.25 to 4.07

*Per modified WHO criteria, two-sided 95% CIs calculated using Clopper-Pearson method.
†Computed using Kaplan-Meier method; medians and two-sided 95% CIs calculated via log-log transformation. Duration of response was defined as time between date of response of confirmed complete response or confirmed partial response (whichever occurred first) and date of progressive disease or death (whichever occurred first).

systemic therapy was received by a similar percentage of patients in both arms of the study. The safety profile of chemotherapy plus ipilimumab was consistent with that in prior chemotherapy plus ipilimumab combination studies,[17,19,23] and no new safety signals were identified. Immune-related toxicities were managed with established safety guidelines, and a majority of grade 2 to 4 immune-related events resolved.

The performance of etoposide and platinum in this trial was consistent with that in previous studies in this patient population (ORR, approximately 60%; median OS, approximately 9.4 months).[3,11] The rationale for this phase III trial was supported by preclinical studies showing synergistic effects of ipilimumab with platinum and etoposide[21,22] and results from the phase II trial of phased ipilimumab in combination with carboplatin and paclitaxel in ED-SCLC.[17] It is unclear why ipilimumab did not confer additional benefit over etoposide and platinum. One possible explanation is that without corresponding T-cell activation in the tumor microenvironment, ipilimumab monotherapy, which stimulates peripheral T-cell activation, may not be effective in mounting a sufficiently strong antitumor response in ED-SCLC. In addition, concomitant chemotherapy may increase immunosuppression, which may be associated with limited T-cell activation and proliferation.

Results from previous efforts to identify prognostic and predictive biomarkers for anti-CTLA4 antibodies have been inconclusive. In melanoma, exploratory studies have suggested that low baseline levels of circulating myeloid-derived suppressor cells, low lactate dehydrogenase levels, low absolute monocyte counts, high levels of circulating regulatory T cells, and high relative lymphocyte counts may be associated with favorable outcomes with ipilimumab.[28-30] However, validation is required in larger patient populations, and not all markers were consistent across tumor types.[31] An in vitro study in SCLC demonstrated that the number and frequency of $CD14^{+}$ HLA–antigen D related/low myeloid-derived suppressor cells could be associated with poor prognosis.[32] A retrospective study of patients with SCLC reported that the ratio of C-reactive protein to albumin could be an independent predictor of OS.[33] Both studies provide early evidence, but further research is required.

Table 3. Treatment-Related AEs Reported in ≥ 5% of Patients Treated With Chemotherapy Plus Ipilimumab or Chemotherapy Plus Placebo

Adverse Event*	No. (%)			
	Chemotherapy Plus Ipilimumab (n = 478)		Chemotherapy Plus Placebo (n = 476)	
	Any Grade	Grade 3 to 5†	Any Grade	Grade 3 to 5‡
Total patients with AE§	391 (82)	231 (48)	361 (76)	214 (45)
Diarrhea	121 (25)	35 (7)	46 (10)	3 (1)
Neutropenia	115 (24)	69 (14)	156 (33)	113 (24)
Anemia	113 (24)	39 (8)	137 (29)	52 (11)
Nausea	109 (23)	7 (1)	75 (16)	3 (1)
Rash	90 (19)	8 (2)	12 (3)	0
Fatigue	62 (13)	11 (2)	53 (11)	1 (< 1)
Decreased appetite	58 (12)	9 (2)	39 (8)	1 (< 1)
Pruritus	55 (12)	3 (1)	8 (2)	0
Neutrophil count decreased	49 (10)	32 (7)	44 (9)	29 (6)
Vomiting	48 (10)	5 (1)	33 (7)	3 (1)
Thrombocytopenia	44 (9)	18 (4)	46 (10)	21 (4)
Leukopenia	27 (6)	7 (1)	52 (11)	17 (4)
Colitis	31 (6)	20 (4)§	1 (< 1)	1 (< 1)
Alopecia	25 (5)	0	35 (7)	1 (< 1)
WBC count decreased	23 (5)	6 (1)	37 (8)	13 (3)
Hemoglobin decreased	25 (5)	5 (1)	14 (3)	3 (1)
Platelet count decreased	20 (4)	8 (2)	24 (5)	4 (1)

Abbreviation: AE, adverse event.
*Includes events with onset on or after day 1 of blinded study therapy and no later than 90 days after last dose of study therapy. Some patients had more than one event.
†Grade 5 events of pneumonia (n = 1), sepsis (n = 1), colitis (n = 1), and ulcerative colitis (n = 1) were reported.
‡Grade 5 events of sepsis (n = 1), multiorgan failure (n = 1), and bone marrow failure (n = 1) were reported.
§One grade 5 event was reported.

A recent report showed that programmed death ligand 1 (PD-L1) is expressed in tumor-infiltrating immune cells in the SCLC stroma, although not in tumor cells,[34] indicating that patients with SCLC with stromal PD-L1 expression may potentially respond to inhibitors of the programmed death-1 (PD-1) immune checkpoint pathway. PD-1 inhibitors nivolumab and pembrolizumab and PD-L1 inhibitors durvalumab and atezolizumab have demonstrated antitumor activity and manageable safety in various tumor types.[35-47] PD-1 inhibitors, which target tumor-infiltrating lymphocytes, complement the antitumor activity of CTLA-4 inhibitors by acting through nonredundant pathways.[20] The combination of nivolumab and ipilimumab has demonstrated synergistic antitumor activity in multiple tumor types, including melanoma and NSCLC.[16,38,48-50]

In patients with PD-L1–positive ED-SCLC who did not respond to first-line therapy, pembrolizumab yielded a 29% ORR, with durable responses (phase I KEYNOTE-028 study; clinical trial information: NCT02054806).[16] Nivolumab alone and in combination with ipilimumab yielded durable objective responses (ORRs of 13% and 31%, respectively), encouraging survival (median OS, 3.6 and 7.8 months, respectively), and manageable safety profiles in heavily pretreated patients with advanced SCLC (phase I/II CheckMate 032 study; clinical trial information: NCT01928394).[15] Other immunotherapeutic agents, including tumor vaccines (eg, polysialic acid, p53-expressing dendritic cells, and Bec2), have had limited success in clinical trials in SCLC.[51]

In conclusion, the addition of ipilimumab to etoposide and platinum did not improve OS compared with etoposide and platinum in chemotherapy-naive patients with ED-SCLC. To date, PD-1 inhibitors, alone or in combination with CTLA-4 inhibitors, show the most promise in SCLC.[15,16] Ongoing approaches include exploring these agents as maintenance after first-line chemotherapy (CheckMate 451 [clinical trial information: NCT02538666], STIMULI [Small Cell Lung Carcinoma Trial With Nivolumab and IpiliMUmab in LImited Disease; clinical trial information: NCT02046733], and a phase II trial of pembrolizumab [clinical trial information: NCT02359019]) or in second-line settings in SCLC (CheckMate 331 [clinical trial information: NCT02481830], KEYNOTE-158 [clinical trial information: NCT02628067], and a phase II study of paclitaxel and pembrolizumab [clinical trial information: NCT02551432]).

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Disclosures provided by the authors are available with this article at www.jco.org.

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Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer

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