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ORIGINAL REPORT

Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

Patients with squamous non–small-cell lung cancer (NSCLC) have poor prognosis and limited treatment options. This randomized, double-blind, phase III study investigated the efficacy and safety of first-line ipilimumab or placebo plus paclitaxel and carboplatin in advanced squamous NSCLC.

Patients and Methods

Patients with stage IV or recurrent chemotherapy-naïve squamous NSCLC were randomly assigned (1:1) to receive paclitaxel and carboplatin plus blinded ipilimumab 10 mg/kg or placebo every 3 weeks on a phased induction schedule comprising six chemotherapy cycles, with ipilimumab or placebo from cycles 3 to 6 and then, after induction treatment, ipilimumab or placebo maintenance every 12 weeks for patients with stable disease or better. The primary end point was overall survival (OS) in patients receiving at least one dose of blinded study therapy.

Results

Of 956 randomly assigned patients, 749 received at least one dose of blinded study therapy (chemotherapy plus ipilimumab, n = 388; chemotherapy plus placebo, n = 361). Median OS was 13.4 months for chemotherapy plus ipilimumab and 12.4 months for chemotherapy plus placebo (hazard ratio, 0.91; 95% CI, 0.77 to 1.07; $P = .25$). Median progression-free survival was 5.6 months for both groups (hazard ratio, 0.87; 95% CI, 0.75 to 1.01). Rates of grade 3 or 4 treatment-related adverse events (TRAEs), any-grade serious TRAEs, and TRAEs leading to discontinuation were numerically higher with chemotherapy plus ipilimumab (51%, 33%, and 28%, respectively) than with chemotherapy plus placebo (35%, 10%, and 7%, respectively). Seven treatment-related deaths occurred with chemotherapy plus ipilimumab, and one occurred with chemotherapy plus placebo.

Conclusion

The addition of ipilimumab to first-line chemotherapy did not prolong OS compared with chemotherapy alone in patients with advanced squamous NSCLC. The safety profile of chemotherapy plus ipilimumab was consistent with that observed in previous lung and melanoma studies. Ongoing studies are evaluating ipilimumab in combination with nivolumab in this population.

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INTRODUCTION

Squamous non–small-cell lung cancer (NSCLC) comprises approximately 30% of all NSCLCs.[1] Platinum-based chemotherapy, the standard first-line treatment for most patients with advanced squamous NSCLC, has limited long-term benefit and is associated with a median overall survival (OS) of only 8 to 11 months.[2-5] The only targeted agent that has shown moderate survival benefit (median OS, 11.5 months) in the first-line setting is the epidermal growth factor receptor antibody necitumumab when combined with chemotherapy.[6] Novel approaches are needed to improve outcomes for this patient population.

Squamous NSCLC has been shown to be a highly immunogenic tumor type[7-13] and is

ASSOCIATED CONTENT

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therefore well-suited for immunotherapy-based regimens. This is supported by the activity of immune checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway (nivolumab, pembrolizumab, and atezolizumab)[14-19] in NSCLC.

Ipilimumab, a cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) inhibitor,[20] has shown activity in several tumor types[21-25] and significantly improved OS in patients with advanced melanoma.[26] CTLA-4 blockade with ipilimumab has been shown to synergize with chemotherapy in preclinical murine tumor models.[27] Ipilimumab combined with chemotherapy has also shown promise in patients; in a phase III trial, ipilimumab plus dacarbazine improved OS versus dacarbazine in patients with advanced melanoma.[28,29]

In a randomized phase II study, patients with chemotherapy-naïve squamous and nonsquamous NSCLC received ipilimumab in phased (in cycles 3 to 6 of six chemotherapy cycles) or concurrent (in cycles 1 to 4 of six chemotherapy cycles) dosing regimens with paclitaxel and carboplatin, followed by ipilimumab maintenance. Ipilimumab administered in the phased regimen significantly prolonged immune-related progression-free survival (irPFS) compared with chemotherapy alone (median, 5.7 *v* 4.6 months, respectively; hazard ratio [HR], 0.72; $P = .05$) and progression-free survival (PFS) by modified WHO (mWHO) criteria (5.1 *v* 4.2 months, respectively; HR, 0.69; $P = .02$). However, ipilimumab administered in the concurrent regimen did not significantly improve irPFS (HR, 0.81; $P = .13$) or mWHO PFS (HR, 0.88; $P = .25$) versus chemotherapy alone.[30] With phased ipilimumab, greater improvements in efficacy were noted in patients with squamous NSCLC (irPFS HR, 0.55; 95% CI, 0.27 to 1.12; mWHO PFS HR, 0.40; 95% CI, 0.18 to 0.87) than in patients with nonsquamous NSCLC (irPFS HR, 0.82; 95% CI, 0.52 to 1.28; mWHO PFS HR, 0.81; 95% CI, 0.53 to 1.26). On the basis of these results, this randomized, double-blind, phase III trial evaluated ipilimumab administered in a phased regimen with carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in patients with chemotherapy-naïve stage IV or recurrent squamous NSCLC (Study 104; ClinicalTrials.gov identifier: NCT01285609).

PATIENTS AND METHODS

Patients

Patients age ≥ 18 years with histologically or cytologically confirmed recurrent or stage IV squamous NSCLC, measurable disease per mWHO criteria,[31,32] an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequate organ function were eligible. Key exclusion criteria included prior systemic therapy for locally advanced or metastatic NSCLC (except radiation therapy or locoregional surgery or adjuvant or neoadjuvant therapy completed ≥ 1 year before enrolling) and a history of brain metastases. Additional exclusion criteria are listed in the Data Supplement.

The protocol was approved by each participating center's ethics committee or institutional review board. The study was run in accordance with Good Clinical Practice (defined by the International Conference on Harmonization) and the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). All patients provided written, informed consent to their participation in the study. An independent data monitoring committee provided study oversight.

Study Design and Treatment

In this multicenter, randomized, controlled, double-blind, phase III study, patients were randomly assigned (1:1) to receive blinded ipilimumab or placebo. Random assignment was stratified by ECOG PS (0 *v* 1), smoking status (heavy smokers [patients who smoked ≥ 10 pack-years] *v* light smokers or nonsmokers [patients who did not meet the criteria to be classified as a heavy smoker]), sex, and region (North America or Western Europe *v* other). The trial had two phases—induction and maintenance (Fig 1A). Induction treatment was paclitaxel 175 mg/m^2 plus carboplatin area under the concentration-time curve 6, both given intravenously (IV) every 3 weeks for six 3-week cycles starting at random assignment, with blinded ipilimumab 10 mg/kg or placebo IV given every 3 weeks for up to four doses, starting at cycle 3. Patients with a complete response (CR), partial response, or stable disease after induction treatment were eligible for maintenance treatment. Maintenance, beginning 9 weeks after the final induction dose of ipilimumab or placebo, comprised blinded ipilimumab 10 mg/kg or placebo IV given every 12 weeks until progressive disease per mWHO criteria[31,32] or unacceptable toxicity, for ≤ 3 years from the first dose of blinded treatment. The dosing schedule for ipilimumab was based on prior phase II and III trials in melanoma[24-26,28] and a prior phase II trial in NSCLC.[30]

In the event of toxicity, protocol-determined paclitaxel and carboplatin dose adjustments and blinded study drug dose delays were allowed; blinded study drug dose reductions were not permitted. Criteria for treatment delay and discontinuation as a result of treatment-related adverse events (TRAEs) are provided in the Data Supplement.

End Points

The primary end point was OS among all randomly assigned patients who received at least one dose of blinded therapy (modified intent-to-treat [mITT] population). Secondary end points were OS among all randomly assigned patients (intent-to-treat [ITT] population) and PFS in the mITT population. Other end points included objective response rate (ORR), duration of response, and safety.

The original primary and secondary end points in the study were OS in the ITT and mITT populations, respectively; however, a pooled, blinded review of the initial data showed a higher than anticipated rate of discontinuation before the initiation of blinded therapy, making any ipilimumab effect difficult to detect in an ITT analysis. To measure the treatment effect of ipilimumab more accurately, the mITT analysis was made the primary analysis through a protocol amendment (on April 2014, at which time enrollment was nearly [98%] complete).

Assessments

Standard baseline assessments are described in the Data Supplement. Tumors were measured using chest and abdomen computed tomography and magnetic resonance imaging scans at baseline; at weeks 7, 13, 19, and 25; and every 12 weeks thereafter until disease progression or end of treatment. Tumor response was assessed by the investigator using mWHO criteria.[31,32] Patients were observed for survival every 12 weeks after treatment discontinuation. Safety was evaluated by monitoring adverse events (AEs) and laboratory parameters until all AEs had resolved, had returned to baseline levels, or were deemed irreversible. Toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[33] AEs of interest consistent with an immune-mediated mechanism (including enterocolitis, dermatitis, hepatitis, endocrinopathies, and neuropathies) and considered drug related by the investigator were classified as immune-related AEs (irAEs).

Statistical Analysis

The study aimed to randomly assign approximately 920 patients (1:1) to the chemotherapy plus ipilimumab and chemotherapy plus placebo arms. Assuming a 24% dropout rate during the first 2 cycles of chemotherapy alone, it was estimated that approximately 700 patients would receive blinded study therapy. The primary analysis was to be performed after at least 518 events had occurred in the mITT population. This number ensured that a two-sided $\alpha = .05$ level test would have 90%

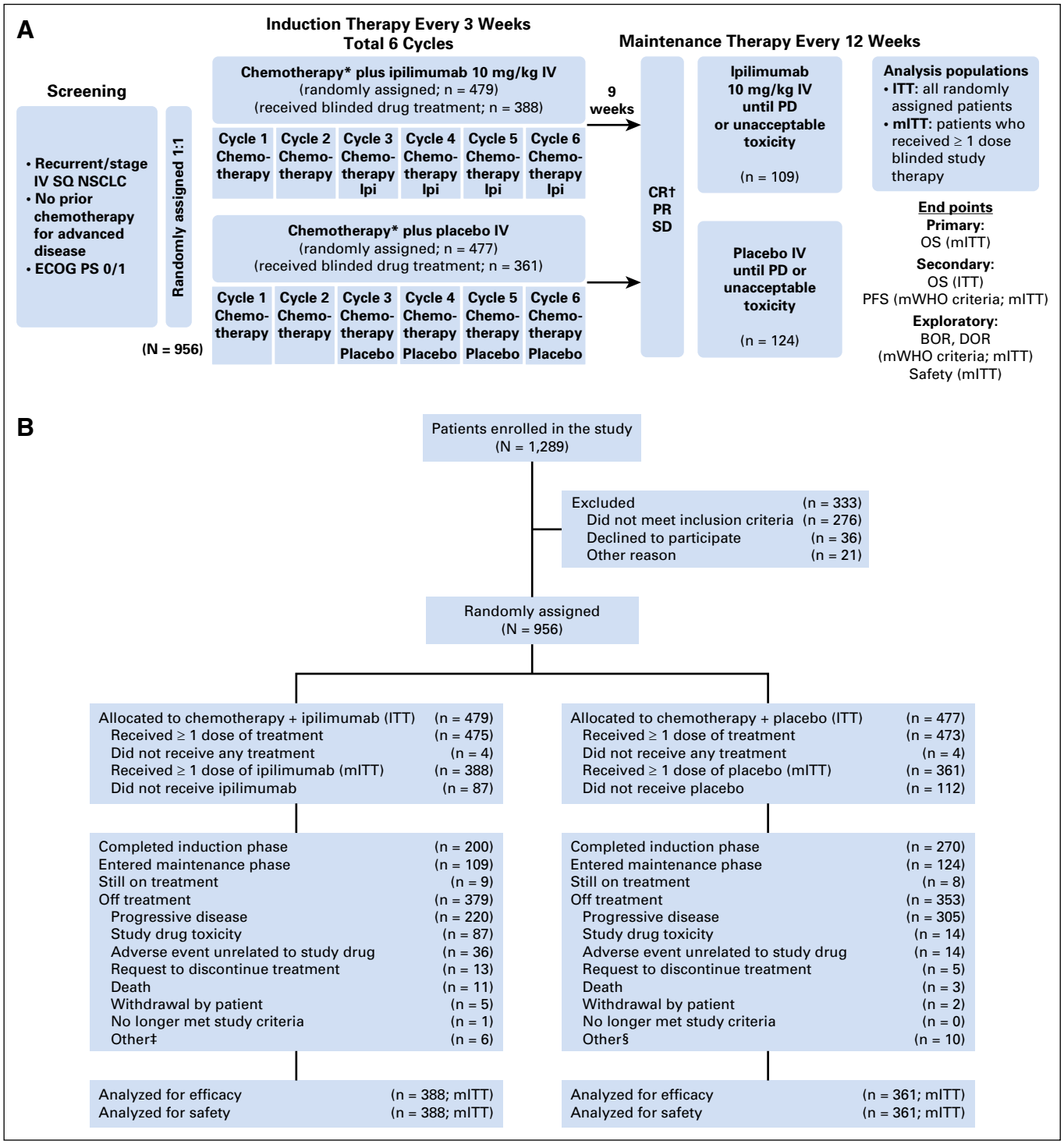

Fig 1. Study design and CONSORT diagram showing patient disposition. (A) Study design. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, sex, and region. Ipilimumab (Ipi) or placebo was administered for a maximum duration of 3 years from first dose of blinded study treatment. (*) Chemotherapy comprised paclitaxel (175 mg/m^2 intravenously [IV] plus carboplatin area under the curve 6 IV) every 3 weeks for up to six doses. (†) Patients with progressive disease (PD) or adverse event leading to discontinuation during the induction phase were observed for toxicity, progression, and overall survival (OS). (B) CONSORT diagram showing disposition of patients with non–small-cell lung cancer (NSCLC) in study 104 as of September 1, 2015. Completed induction phase indicates that a patient completed the induction phase without entering the maintenance phase. (‡) Of these six patients, two patients had maximum clinical benefit. (§) Of these 10 patients, four patients had maximum clinical benefit, results were not reported for two patients, and two patients were noncompliant. BOR, best overall response; CR, complete response; DOR, duration of response; ITT, intent-to-treat; mITT, modified intent-to-treat (defined as the population who received at least one dose of randomly assigned study drug); mWHO, modified WHO; PFS, progression-free survival; PR, partial response; SD, stable disease; SQ, squamous.

power if the true HR for the first 2 cycles was 1 and the HR after blinded therapy initiation was 0.75. A median OS of 10 months in the chemotherapy plus placebo arm after 2 cycles of chemotherapy was also assumed. As a second condition, at least 705 events in the ITT population were required for the database to be locked (per the original study design). Statistical considerations for the ITT population are included in the Data Supplement.

OS was defined as the time from random assignment until death. For patients who did not die, OS was censored at the last date they were known to be alive. In the mITT population, OS and PFS between treatment arms were compared using an unstratified, two-sided, log-rank test; the HR and corresponding 95% CIs were estimated using an unstratified Cox model with treatment arm as the only covariate. OS and PFS distributions were estimated using the Kaplan-Meier method. ORR per mWHO was calculated for each treatment arm, with corresponding 95% CIs calculated using the Clopper-Pearson method.

After a crossing of the OS curves was observed, a post-hoc analysis was conducted to examine the proportional hazards assumption for OS by testing for a treatment-period interaction, with period defined as a binary variable (before or after the time point when the curves crossed). A piecewise hazards model was used to provide estimates of the HR over time (ie, before, during, and after the crossover of the survival curves).

RESULTS

Patients and Treatment

Between August 2011 and June 2015, 1,289 patients were assessed for eligibility, and 956 patients at 233 sites in 34 countries were randomly assigned to receive paclitaxel and carboplatin plus ipilimumab (chemotherapy plus ipilimumab; n = 479) or paclitaxel and carboplatin plus placebo (chemotherapy plus placebo; n = 477; Figs 1A and 1B). Four patients in each arm did not receive any treatment, and 87 patients (18%) and 112 patients (24%) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively, discontinued treatment before receiving the blinded study drug, most commonly because of progressive disease (Data Supplement). This report focuses on efficacy and safety analyses in randomly assigned patients who received at least one dose of the blinded study drug (mITT population), including 388 patients (81%) and 361 patients (76%) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively. Baseline characteristics and OS in the ITT population are presented in the Data Supplement.

Baseline characteristics in the mITT population were generally well balanced between treatment arms (Table 1). Median age was 64 years (range, 28 years to 85 years). Most patients were male (85%), white (69%), and heavy smokers (88%), and had an ECOG PS of 1 (65%). The median number of blinded study drug doses received in the induction and maintenance phases was similar in the chemotherapy plus ipilimumab arm (four doses; range, one to 15 doses) and chemotherapy plus placebo arms (four doses; range, one to 12 doses). However, only 52% of patients in the chemotherapy plus ipilimumab arm received the four planned blinded therapy induction doses compared with 76% of patients in the chemotherapy plus placebo arm (Data Supplement). Exposure to chemotherapy was lower in the chemotherapy plus ipilimumab arm (median, five doses received; range, one to seven doses received) than in the chemotherapy plus placebo arm (median, six doses received; range, one to seven doses received; Data Supplement). A total of 109 patients (28%) and 124 patients (34%) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively, started maintenance treatment; at the time of analysis, nine patients (2%) and eight patients (2%) in each arm remained on treatment (Data Supplement). After discontinuing study treatment, 183 patients (47%) and 207 patients (57%) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively, received subsequent chemotherapy or immunotherapy (Data Supplement).

Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy (mITT population)

Characteristic	Chemotherapy Plus Ipilimumab (n = 388) No.	%	Chemotherapy Plus Placebo (n = 361) No.	%
Median age, years (range)	64 (28-84)		64 (28-85)	
Age category, years				
≤ 64	198	51	182	50
≥ 65 to ≤ 74	152	39	146	40
≥ 75	38	10	33	9
Sex				
Male	326	84	309	85
Female	62	16	52	14
Race				
White	276	71	243	67
Asian	106	27	108	30
Black/African American	3	1	3	1
Other	2	< 1	7	2
Region				
North America/Western Europe	202	52	183	51
Other*	186	48	178	49
ECOG PS				
0	135	35	124	34
1	251	65	234	65
≥ 2†	2	< 1	3	1
Disease stage				
IV	367	95	333	92
Recurrent	21	5	28	8
Smoking status				
Heavy smoker‡	339	87	317	88
Former/light/nonsmoker§	44	11	39	11
Unknown	5	1	5	1
Median time from diagnosis to first study dose, months (range)	1.0 (0.1-85.1)		1.0 (0.1-87.6)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; PS, performance status.
*Includes Australia and countries in Asia, Eastern Europe, and South America.
†ECOG PS ≥ 2 was an exclusion criterion.
‡Defined as ≥ 10 pack-years.
§Patients who did not meet the definition for heavy smoker.

Efficacy

At database lock (September 1, 2015), 553 patients (74%) had died. The median follow-up time for survival was 12.5 months for the chemotherapy plus ipilimumab arm and 11.8 months for the chemotherapy plus placebo arm. The study did not meet its primary end point; there was no statistically significant difference in OS between the two treatment arms in the mITT population (HR, 0.91; 95% CI, 0.77 to 1.07; log-rank $P = .25$; Fig 2A). The Kaplan-Meier curves suggested nonproportional hazards, with the

curve for the ipilimumab arm initially lying below that for the placebo arm, but crossing at approximately 10 months and remaining above the placebo arm thereafter. A test for a treatment-period interaction (before 10 months and after) verified that the proportionality assumption was violated ($P = .024$). This prompted the development of an exploratory piecewise hazards model to estimate the HR over the following three different time periods: before 8 months, between 8 and 16 months, and after 16 months; the estimated HRs for these time periods were 1.44 (95% CI, 1.08 to 1.92), 0.67 (95% CI, 0.52 to 0.86), and 0.84 (95% CI, 0.57 to 1.23), respectively.

In the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, median OS was 13.4 months (95% CI, 11.8 months to 14.8 months) and 12.4 months (95% CI, 11.6 months to 13.6 months), respectively; 1-year OS rates were 54% and 53%, respectively; and 2-year OS rates were 24% and 18%, respectively. The HRs for OS across predefined patient

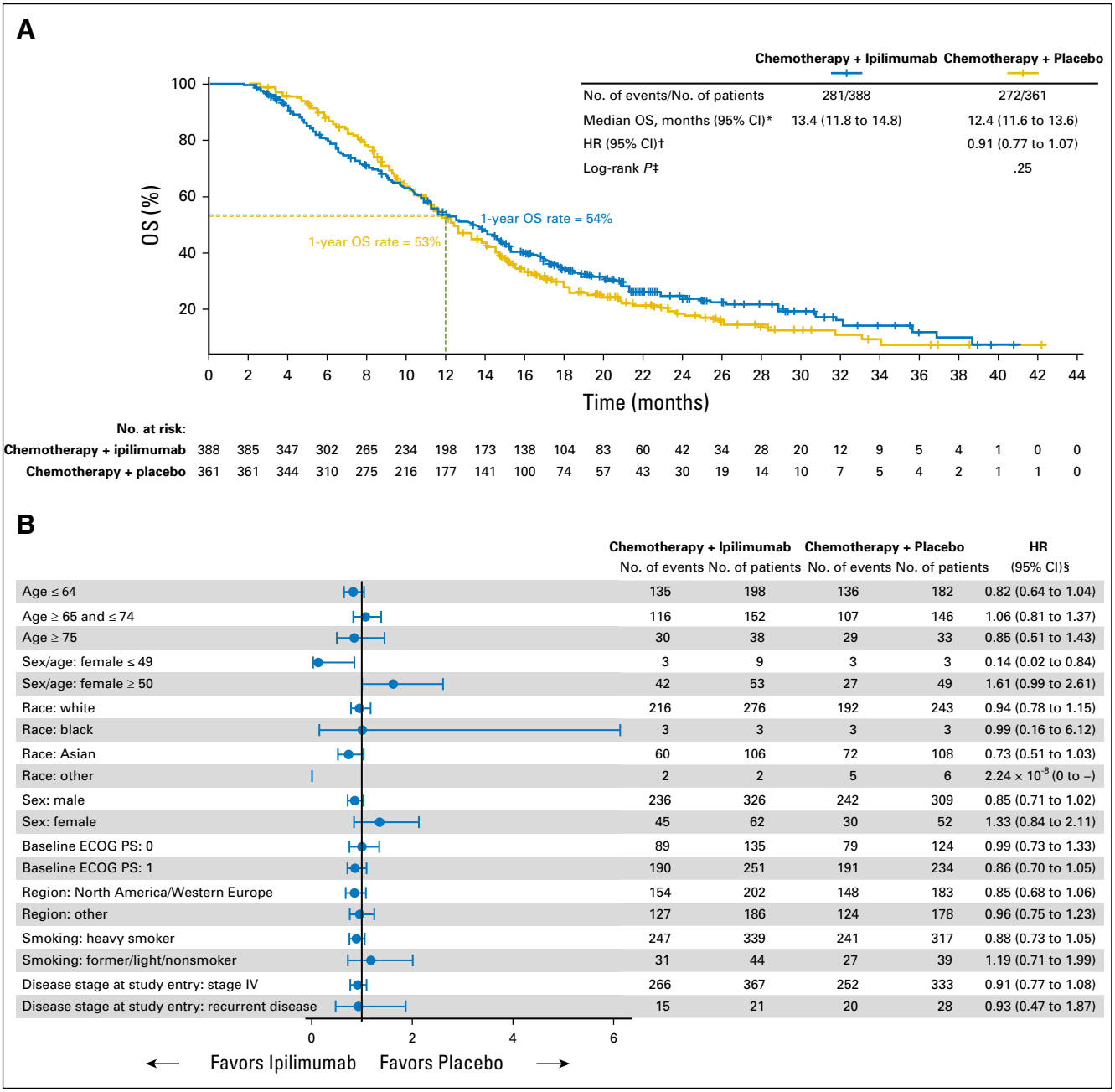

Fig 2. Overall survival (OS) in the modified intent-to-treat (mITT) population and in predefined patient subgroups. (A) Kaplan-Meier plot of OS. OS was defined as the time from the date of random assignment until the date of death. Symbols indicate patients who had not died or who were lost to follow-up and who were thus censored on the last date known to be alive. (*) Median and associated two-sided 95% CI calculated via log-log transformation. (†) Hazard ratio (HR) of ipilimumab over placebo with a two-sided 95% CI is based on an unstratified Cox proportional hazards model with treatment as the single covariate. (‡) On the basis of an unstratified two-sided log-rank test. (B) Treatment effect on OS in predefined patient subgroups on the basis of an unstratified Cox proportional hazards model for patients in each indicated subgroup. (§) HR and two-sided 95% CIs were calculated as indicated earlier. ECOG, Eastern Cooperative Oncology Group; PS, performance status.

subgroups generally did not seem to favor one treatment over the other (Fig 2B).

PFS did not differ between the treatment arms (HR, 0.87; 95% CI, 0.75 to 1.01; unstratified log-rank $P = .07$), and the Kaplan-Meier curves suggested nonproportional hazards (Fig 3). Median PFS was 5.6 months (95% CI, 5.4 months to 5.9 months) with chemotherapy plus ipilimumab and 5.6 months (95% CI, 5.5 months to 5.7 months) with chemotherapy plus placebo.

ORRs were 44% (including one CR) and 47% (including two CRs) in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively; median duration of response was numerically higher in the chemotherapy plus ipilimumab arm than in the chemotherapy plus placebo arm (5.7 months [95% CI, 5.1 months to 6.7 months] *v* 4.7 months [95% CI, 4.3 months to 5.6 months], respectively; Table 2). Stable disease occurred in 37% and 47% of patients in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively.

Safety

TRAEs occurred in 89% (grade 3 to 5, 53%) and 81% (grade 3 to 5, 36%) of patients in the chemotherapy plus ipilimumab and chemotherapy plus placebo arms, respectively (Table 3). The most common grade 3 or 4 TRAEs were neutropenia (14%), anemia (12%), diarrhea (7%), and thrombocytopenia (7%) in the chemotherapy plus ipilimumab arm. Neutropenia (14%), anemia (7%), and thrombocytopenia (4%) were the most common grade 3 or 4 TRAEs in the chemotherapy plus placebo arm. Serious TRAEs occurred more frequently with chemotherapy plus ipilimumab than with chemotherapy plus placebo (any grade, 33% *v* 10%, respectively; grade 3 to 5, 28% *v* 9%, respectively; Data Supplement). In the chemotherapy plus ipilimumab arm, there were seven treatment-related deaths as a result of acute hepatic failure, acute kidney insufficiency, anemia, intestinal perforation, ischemic colitis, multiorgan failure, and pneumonia (n = 1 for each). In the chemotherapy plus placebo arm, one patient died as a result of treatment-related sepsis with septic shock. Discontinuations as a result of TRAEs were more frequent in the chemotherapy plus ipilimumab arm than the chemotherapy plus placebo arm (any grade, 28% *v* 7%, respectively; grade 3 or 4, 20% *v* 3%, respectively; Data Supplement). The most common TRAEs leading to discontinuation were diarrhea (6%), colitis (3%), peripheral sensory neuropathy (2%), and anemia (2%) in the chemotherapy plus ipilimumab arm. The most common TRAE leading to discontinuation was peripheral sensory neuropathy (1%) in the chemotherapy plus placebo arm.

The most common irAEs in the chemotherapy plus ipilimumab arm were dermatologic (36%), GI (28%), and neurologic (27%) in nature; the most frequently reported individual irAEs were diarrhea (27% *v* 11% in the chemotherapy plus placebo arm), rash (17% *v* 4% in the chemotherapy plus placebo arm), and pruritus (14% *v* 2% in the chemotherapy plus placebo arm; Data Supplement). Endocrine irAEs were reported in 9% of patients in the chemotherapy plus ipilimumab arm and included decreased thyroid-stimulating hormone levels (3%), hyperthyroidism (2%), and adrenal insufficiency (1%). The median time to onset (from the first blinded study therapy dose) of grade 2 to 5 irAEs in the chemotherapy plus ipilimumab arm ranged from approximately 4 weeks for GI, neurologic, and skin events to 12 weeks for endocrine events (Data Supplement). Most grade 2 to 4 irAEs (186 of 264 patients; 70%) had resolved by time of analysis (Data Supplement).

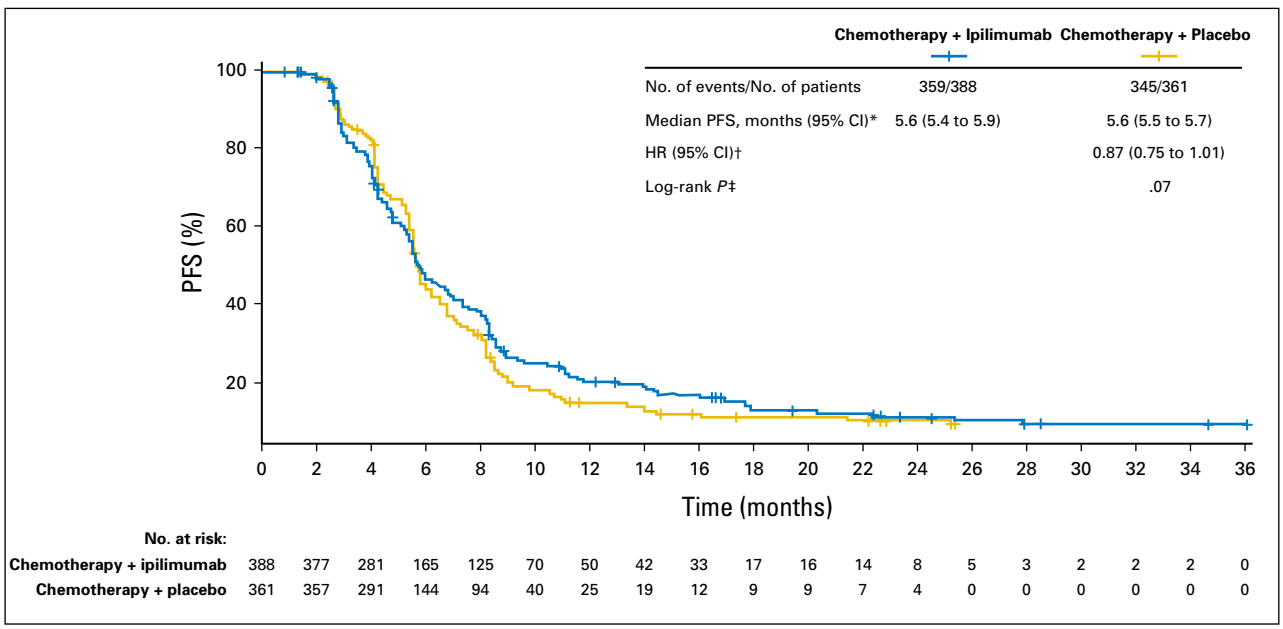

Fig 3. Kaplan-Meier plot of progression-free survival (PFS) per modified WHO (mWHO) criteria in the modified intent-to-treat population. An increase in target lesions of ≥ 25% from baseline, progression of nontarget lesions, or the presence of a new lesion (measurable or not) is considered progression by mWHO criteria. (*) Median PFS and associated two-sided 95% CI calculated via log-log transformation. (†) Hazard of ipilimumab over hazard of placebo with a two-sided 95% CI is based on an unstratified Cox proportional hazards model with treatment as the single covariate. (‡) On the basis of an unstratified two-sided log-rank test. HR, hazard ratio.

Table 2. Tumor Response (mITT population)

Activity	Chemotherapy Plus Ipilimumab (n = 388)	Chemotherapy Plus Placebo (n = 361)
Objective response rate, %*	44	47
95% CI	39 to 49	42 to 52
Best overall response, No. (%)		
Complete response	1 (< 1)	2 (< 1)
Partial response	171 (44)	167 (46)
Stable disease	142 (37)	150 (42)
Progressive disease	54 (14)	36 (10)
Unknown	20 (5)	6 (2)
Median duration of response, months†	5.7	4.7
95% CI	5.1 to 6.7	4.3 to 5.6

Abbreviation: mITT, modified intent-to-treat.
*Per modified WHO criteria; two-sided 95% CI calculated by the Clopper-Pearson method.
†Computed using the Kaplan-Meier method; median and two-sided 95% CI calculated via log-log transformation.

DISCUSSION

To our knowledge, this is the largest phase III trial of a first-line immune checkpoint inhibitor conducted in patients with advanced squamous NSCLC. The trial did not meet its primary end point; the addition of ipilimumab to chemotherapy as first-line treatment did not result in a statistically significant improvement in OS versus chemotherapy alone. This result was generally consistent across predefined patient subgroups. Similarly, secondary efficacy end points, including OS in all randomly assigned patients, PFS, and ORR, did not differ between treatment arms.

The overall safety profile of chemotherapy plus ipilimumab was consistent with that reported in previous phase III studies in melanoma and SCLC[28,34] and the phase II trial in NSCLC.[30] No new safety concerns were identified. Immune-related toxicities were manageable using established safety guidelines. However, in the chemotherapy plus ipilimumab arm, compared with the chemotherapy plus placebo arm, there were higher rates of grade 3 to 5 TRAEs (53% *v* 36%, respectively) and discontinuation as a result of TRAEs (28% *v* 7%, respectively).

The toxicity and high treatment discontinuation rates in the chemotherapy plus ipilimumab arm seem to have affected the extent of exposure to chemotherapy, in addition to ipilimumab. In fact, exposure to chemotherapy was lower in the chemotherapy plus ipilimumab arm; only 46% of patients in the chemotherapy plus ipilimumab arm received all six doses of chemotherapy versus 67% of patients in the chemotherapy plus placebo arm. Consequently, survival in this arm may have been affected, with fewer

Table 3. Treatment-Related Adverse Events Reported in ≥ 5% of Patients in Either Treatment Arm (mITT population)

	Chemotherapy Plus Ipilimumab (n = 388)				Chemotherapy Plus Placebo (n = 361)			
	Any Grade		Grade 3 to 5†		Any Grade		Grade 3 to 5‡	
Adverse Event*	No.	%	No.	%	No.	%	No.	%
Any adverse event	344	89	205	53	292	81	129	36
Anemia	114	29	46	12	91	25	27	7
Diarrhea	105	27	28	7	38	11	6	2
Neutropenia	70	18	55	14	70	19	50	14
Decreased appetite	67	17	6	2	43	12	5	1
Rash	67	17	8	2	14	4	0	0
Thrombocytopenia	65	17	28	7	59	16	13	4
Nausea	62	16	1	< 1	46	13	0	0
Fatigue	60	15	12	3	59	16	10	3
Pruritus	56	14	4	1	8	2	0	0
Peripheral sensory neuropathy	44	11	6	2	63	17	5	1
Peripheral neuropathy	36	9	3	1	34	9	1	< 1
Alopecia	34	9	0	0	29	8	0	0
Platelet count decreased	34	9	7	2	25	7	8	2
Asthenia	33	9	7	2	18	5	5	1
Vomiting	33	9	2	< 1	26	7	3	1
Pyrexia	31	8	1	< 1	9	2	0	0
Arthralgia	27	7	0	0	16	4	0	0
Leukopenia	27	7	10	3	30	8	10	3
Myalgia	27	7	0	0	25	7	1	< 1
Hemoglobin decreased	26	7	12	3	17	5	5	1
ALT increased	25	6	7	2	4	1	0	0
AST increased	21	5	4	1	6	2	2	< 1
Neutrophil count decreased	18	5	11	3	19	5	12	3
WBC count decreased	15	4	0	0	21	6	6	2

Abbreviation: mITT, modified intent-to-treat.
*Includes events with onset on or after day 1 of blinded study therapy and no later than 90 days after the last dose of study therapy.
†Seven patients had grade 5 treatment-related adverse events, including acute hepatic failure, acute kidney insufficiency, anemia, intestinal perforation, ischemic colitis, multiorgan failure, and pneumonia (n = 1 each).
‡One patient had a grade 5 treatment-related adverse event, which was sepsis with septic shock.

patients in the chemotherapy plus ipilimumab arm able to benefit from chemotherapy compared with the control arm. The higher initial mortality observed in the chemotherapy plus ipilimumab arm versus the control arm was probably also a result of the reduced exposure to chemotherapy during the induction phase. This increased initial mortality in the chemotherapy plus ipilimumab arm combined with the delayed long-term effects of ipilimumab may have, in turn, led to the crossing of the OS curves at 10 months. In summary, the reduced chemotherapy exposure, triggered by the toxicity and higher discontinuation rates in the chemotherapy plus ipilimumab arm, potentially contributed to the failure of the study.

The results of this study mirror those of a similar phase III trial in patients with chemotherapy-naïve extensive-stage small-cell lung cancer (SCLC; ClinicalTrials.gov identifier: NCT01450761)[34] in which the addition of phased ipilimumab to chemotherapy failed to improve OS compared with chemotherapy alone. It was hypothesized that ipilimumab, which stimulates early-stage T-cell activation in the lymphoid compartment, may not generate a sufficiently strong antitumor response in SCLC without corresponding effector T-cell stimulation within the localized tumor microenvironment.[35] This explanation may also hold true for squamous NSCLC. Supporting this premise, robust activity of the combination of ipilimumab and nivolumab (which activates T-cell function in the tumor microenvironment) was noted in patients with recurrent SCLC.[36] Squamous NSCLC, like SCLC, has a high mutational burden and is therefore a good PD-1 target.[37,38] Survival benefit with PD-1 inhibitors has been observed in NSCLC in the previously treated[14-16,18,19] and first-line settings.[17,39,40] In a phase I study, first-line nivolumab plus ipilimumab showed promising activity and manageable safety in patients with advanced NSCLC.[41]

On the basis of the activity and safety profile of the nivolumab plus ipilimumab combination observed in both NSCLC[41] and melanoma,[42] combining PD-1 inhibition with CTLA-4 checkpoint inhibition may represent a promising strategy for first-line treatment of squamous NSCLC. Ongoing studies are evaluating PD-1 inhibitors in combination with other agents, including platinum-based chemotherapy and CTLA-4 inhibitors, and newer agents (OX-40, lymphocyte activation gene 3 protein, and T-cell immunoglobulin and mucin domain 3 inhibitors) in the first-line treatment of NSCLC.

In conclusion, phased ipilimumab in combination with chemotherapy did not improve survival versus chemotherapy alone as first-line treatment of squamous NSCLC. Combination immunotherapy regimens and other agents in development offer more effective treatment options for this patient population.

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

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Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer

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