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ORIGINAL REPORT

Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study

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See accompanying editorial on page 2025 and articles on pages 2055 and 2063

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ABSTRACT

Purpose
Ipilimumab, which is an anti–cytotoxic T-cell lymphocyte-4 monoclonal antibody, showed a survival benefit in melanoma with adverse events (AEs) managed by protocol-defined guidelines. A phase II study in lung cancer assessed the activity of ipilimumab plus paclitaxel and carboplatin.

Patients and Methods
Patients (N = 204) with chemotherapy-naive non–small-cell lung cancer (NSCLC) were randomly assigned 1:1:1 to receive paclitaxel (175 mg/m^2) and carboplatin (area under the curve, 6) with either placebo (control) or ipilimumab in one of the following two regimens: concurrent ipilimumab (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin) or phased ipilimumab (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin).Treatment was administered intravenously every 3 weeks for ≤ 18 weeks (induction). Eligible patients continued ipilimumab or placebo every 12 weeks as maintenance therapy. Response was assessed by using immune-related response criteria and modified WHO criteria. The primary end point was immune-related progression-free survival (irPFS). Other end points were progression-free survival (PFS), best overall response rate (BORR), immune-related BORR (irBORR), overall survival (OS), and safety.

Results
The study met its primary end point of improved irPFS for phased ipilimumab versus the control (hazard ratio [HR], 0.72; $P = .05$), but not for concurrent ipilimumab (HR, 0.81; $P = .13$). Phased ipilimumab also improved PFS according to modified WHO criteria (HR, 0.69; $P = .02$). Phased ipilimumab, concurrent ipilimumab, and control treatments were associated with a median irPFS of 5.7, 5.5, and 4.6 months, respectively, a median PFS of 5.1, 4.1, and 4.2 months, respectively, an irBORR of 32%, 21% and 18%, respectively, a BORR of 32%, 21% and 14%, respectively, and a median OS of 12.2, 9.7, and 8.3 months. Overall rates of grade 3 and 4 immune-related AEs were 15%, 20%, and 6% for phased ipilimumab, concurrent ipilimumab, and the control, respectively. Two patients (concurrent, one patient; control, one patient) died from treatment-related toxicity.

Conclusion
Phased ipilimumab plus paclitaxel and carboplatin improved irPFS and PFS, which supports additional investigation of ipilimumab in NSCLC.

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INTRODUCTION

Platinum-based chemotherapy combinations are the standard of first-line care for patients with advanced non–small-cell lung cancer (NSCLC) with a median overall survival (OS) that ranges from 8 to 12 months.[1,2] Recent additions to the standard chemotherapy of biologics, such as bevacizumab and cetuximab, have made only modest differences in survival, which necessitated new therapeutic paradigms.[3-6] One anticancer target of current interest is cytotoxic T-lymphocyte antigen-4 (CTLA-4), which is a negative regulator of T-cell activation.[7-10]

Ipilimumab, which is a fully human monoclonal antibody, specifically blocks the binding of CTLA-4 to its ligands (CD80/CD86). This blockade augments T-cell activation and proliferation, which leads to tumor infiltration by T cells and tumor regression.[11-18] Early clinical trials with ipilimumab have shown activity in a broad range of cancers.[19-25] In recent phase 3 trials, ipilimumab was the first agent to demonstrate a statistically significant improvement in OS in patients with previously treated (hazard ratio [HR], 0.66; $P = .003$) as wells as previously untreated metastatic melanoma (HR, 0.72; $P < .001$).[26,27] Treatment-related adverse events (AEs) that occurred in ≥15% of patients included pruritus, rash, and diarrhea, and most immune-related AEs (irAEs) were managed by using drug-specific treatment guidelines.[26,27]

To assess the activity of ipilimumab in patients with lung cancer, we designed a randomized phase II study that compared ipilimumab plus paclitaxel and carboplatin with paclitaxel and carboplatin alone. The rationale for the combination of ipilimumab with paclitaxel and carboplatin was based on several considerations. First, paclitaxel and carboplatin is a commonly used first-line combination for NSCLC and is generally well tolerated.[2,4,28] Second, in preclinical models, chemotherapeutics that included taxanes and platinum-based compounds induced the release of tumor-specific antigens from dying tumor cells, which initiated T-cell activation.[29-34] Third, these agents sensitized tumor cells to lymphocyte-mediated killing in animal models of tumors.[35] Finally, certain chemotherapeutics have been shown to enhance the antitumor activity of the anti–CTLA-4 antibody in preclinical tumor models.[36,37]

Because the sequence of the administration of chemotherapy and immunotherapy has been shown to affect outcome,[34,38,39] two alternate regimens of drug administration were used in this study. In the concurrent regimen, ipilimumab was administered concurrently with paclitaxel and carboplatin, which allowed ipilimumab to be present at the earliest phase of chemotherapy-induced antigen release. In the phased regimen, paclitaxel and carboplatin was given before ipilimumab, which allowed antigen release to occur before ipilimumab addition.

Both patients with NSCLC and extensive disease–small-cell lung cancer (ED-SCLC) were enrolled onto the study, which was designed to analyze NSCLC and ED-SCLC cohorts separately. This report describes the NSCLC cohort. Data for the ED-SCLC cohort have been presented elsewhere.[40]

PATIENTS AND METHODS

Study Design and Treatment

This was a randomized, double-blind, international, multicenter phase II study in previously untreated patients with lung cancer. The study population included patients with NSCLC or ED-SCLC, and random assignment was stratified by tumor type and study site. Given the relatively low incidence of ED-SCLC, the study was planned such that enrollment was stopped when the target number of patients with NSCLC (approximately 210 patients) was reached along with a minimum number of patients with ED-SCLC (approximately 120 patients). This report focuses on the NSCLC patients.

Patients were randomly assigned 1:1:1 to receive a concurrent ipilimumab regimen (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin), a phased ipilimumab regimen (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin), or a control regimen (up to six doses of placebo plus paclitaxel and carboplatin). Ipilimumab (10 mg/kg) or placebo, paclitaxel (175 mg/m^2), and carboplatin (area under the curve, 6) were administered intravenously once every 3 weeks for a maximum of 18 weeks during the induction phase starting on day 1. The paclitaxel dose was chosen on the basis of phase II data that showed that the response rate and survival with a paclitaxel dose of 175 mg/m^2 did not differ significantly from the response rate and survival with a paclitaxel dose of 225 mg/m^2, although the dose of 175 mg/m^2 showed better safety.[28] The lower dose offered the possibility of lower additive toxicity when administered with ipilimumab. Patients without progression who continued to tolerate treatment received maintenance treatment with either ipilimumab (ipilimumab arms) or placebo (control arm) once every 12 weeks until progression, death or intolerance.

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by local ethics committees. Informed consent was provided by all patients before enrollment.

Patients

Eligible patients were men and women age ≥18 years who had histologically or cytologically confirmed NSCLC with stage IIIB/IV or recurrent disease, received no previous systemic therapy for lung cancer, had a measurable tumor lesion, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Exclusion criteria were as follows: receipt of CD137 agonists or CTLA-4 modulators; uncontrolled malignant pleural effusion; brain metastases; current malignancies or previous malignancies within 5 years; autoimmune disease; peripheral neuropathy of grade 2 or higher; inadequate hematologic, hepatic, or renal function; or chronic use of immunosuppressive drugs and/or systemic corticosteroids (except for use as premedication for paclitaxel infusion or for toxicity management).

Study Assessments

Tumor assessments were conducted by using radiologic imaging and were performed at screening and every 6 weeks during the induction phase and every 12 weeks during the maintenance phase. Response was assessed by a blinded independent radiologic review committee by using modified WHO criteria (mWHO) and newly proposed immune-related response criteria (irRC). Assessments by investigators on the basis of irRC were used to guide clinical care. The irRC was developed from mWHO to better capture unique response patterns to ipilimumab that included regression of index lesions in the face of new lesions and initial progression followed by tumor stabilization or decrease in tumor burden.[41,42] To account for these patterns, the irRC used the total tumor burden obtained by adding measurable new lesions to index lesions in determining the tumor response. Changes in nonindex or nonmeasurable lesions were not considered in the determination of response by irRC. Thresholds for immune-related complete response (irCR, complete disappearance of all lesions), immune-related partial response (irPR; decrease of total tumor burden from baseline by ≥ 50%), immune-related progressive disease (irPD; increase of total tumor burden from nadir by ≥ 25%), and immune-related stable disease (all other settings including a slow steady decline in total tumor burden from baseline) were the same as for the complete response (CR), partial response (PR), progressive disease (PD), and stable disease per mWHO. Details of the irRC are described elsewhere.[41] Responses by both criteria were confirmed by two evaluations ≥ 4 weeks apart. Assessments were performed until investigator-documented progression or unacceptable toxicity. Patients without progression who discontinued treatment for toxicity were followed until they received alternative therapy or withdrew consent.

AEs and immune-related AEs (irAEs) were evaluated continuously starting from the first dose of the study drug to a minimum of 70 days after the last dose. irAE was defined as an AE that was treatment-related and consistent with an immune-mediated event. AEs, irAEs, and laboratory values were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Guidelines for the management of irAEs included the administration of corticosteroids (orally or intravenously), a delay in a scheduled dose, or discontinuation of therapy. No dose reductions were allowed for ipilimumab.

Ipilimumab dosing was skipped in the case of grade 2 or higher nondermatologic AEs, grade 3 or higher dermatologic AEs, or grade 3 or higher hematologic abnormalities until the event improved to grade 1 or less; if the event did not improve to grade 1 or less, the treatment was discontinued permanently. Dose modifications for paclitaxel and carboplatin were made according to the package inserts/product label.[43,44] Discontinuation or interruption of ipilimumab did not preclude the continuation of paclitaxel or carboplatin and vice versa.

Statistical Analysis

Efficacy parameters were analyzed in all randomly assigned patients by using SAS software (version 8.2, 2001; SAS Institute, Cary, NC). Safety analysis involved patients who received at least one dose of any study drug. The primary efficacy end point in the study was immune-related progression-free survival (irPFS; time from randomization to irPD or death). Key secondary end points included modified WHO criteria progression-free survival (mWHO-PFS); (time from randomization to PD per mWHO or death), OS (time from randomization to death), immune-related best overall response rate (irBORR; proportion of patients with irCR or irPR), modified WHO criteria best overall response rate (mWHO-BORR; proportion of patients with CR or PR per mWHO), immune-related disease control rate (irDCR; proportion of patients with irCR, irPR, or immune-related stable disease), modified WHO criteria disease control rate (mWHO-DCR; proportion of patients with CR, PR, or stable disease per mWHO). irPFS, mWHO-PFS, and OS were compared between each ipilimumab arm and the control arm by using an unstratified log-rank test with one-sided α of 0.1. No multiplicity adjustments to α were made. No analysis by study site was conducted. By assuming an exponential distribution for irPFS, it was estimated that 150 events of 210 randomized patients with NSCLC among three arms would provide 90% power to detect a difference in irPFS (HR, 0.6; median for control arm, 4.5 months) with a one-sided α of 0.1. Likewise, 100 deaths would provide 57% power to detect a difference in OS (HR, 0.74; median for control arm, 10 months). irPFS, mWHO-PFS, and OS were estimated by using the Kaplan-Meier product-limit method; medians were estimated with their 95% CIs calculated according to the method of Brookmeyer and Crowley.[45] HRs with 95% CIs were estimated for irPFS, mWHO-PFS, and OS by using an unstratified Cox proportional hazards model. irBORR, BORR, irDCR, and DCR were estimated, and their 95% CIs were computed, according to the method of Clopper and Pearson.[46] All 95% CIs were two-sided. Patient follow-up for OS continued beyond the primary database lock.

RESULTS

Patients and Treatment

Two hundred four patients with previously untreated NSCLC were randomized between February 2008 and February 2009 at 54 sites across eight countries, and 203 patients were treated (Fig 1). At

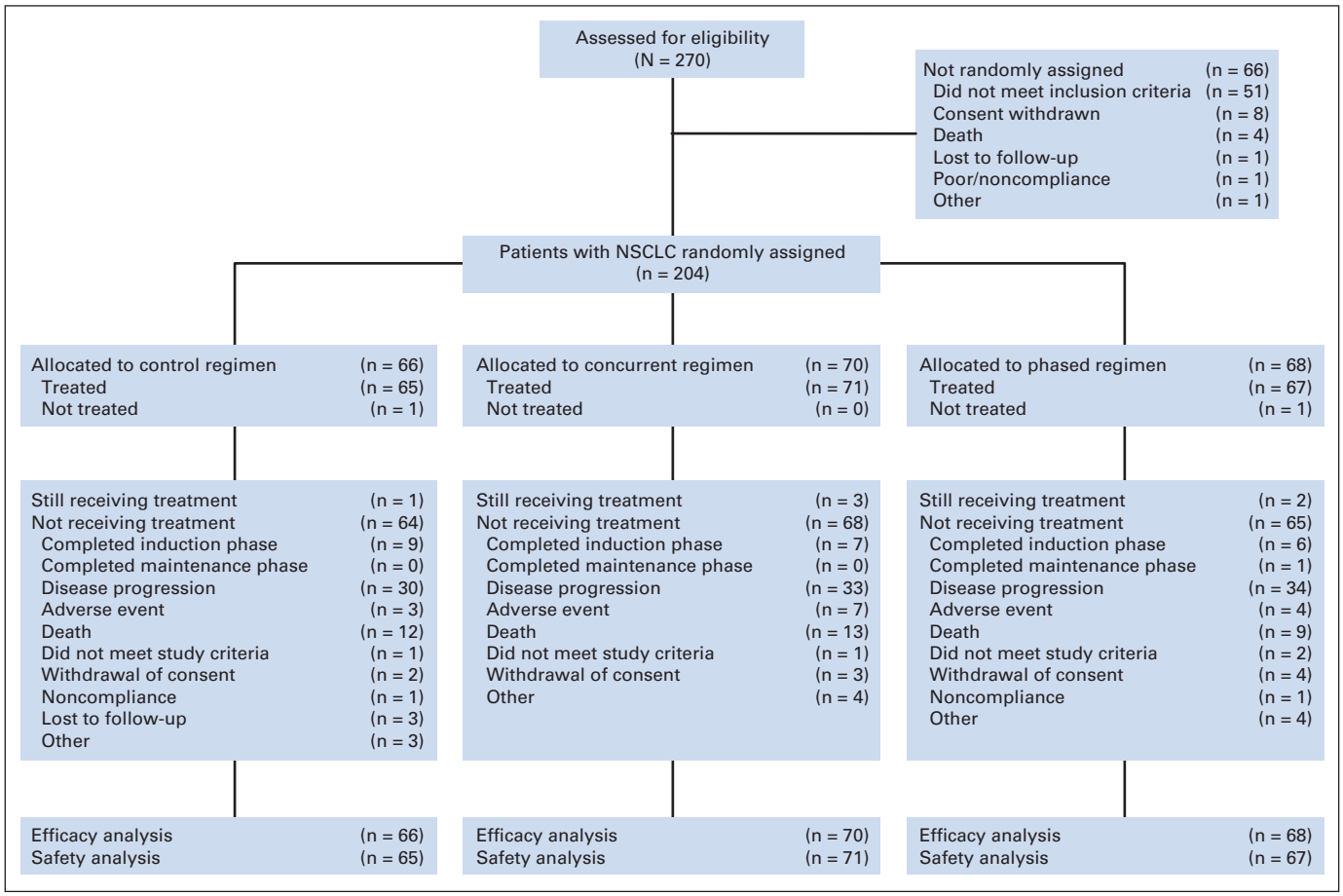

Fig 1. Disposition of patients with non–small-cell lung cancer (NSCLC) in study CA184-041 as of August 24, 2010. Patients were randomly assigned to a control regimen (up to six doses of placebo plus paclitaxel and carboplatin), concurrent ipilimumab regimen (four doses of ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin), or phased ipilimumab regimen (two doses of placebo plus paclitaxel and carboplatin followed by four doses of ipilimumab plus paclitaxel and carboplatin). Patients who discontinued treatment may have differentially discontinued one or more study therapies and may have received paclitaxel and/or carboplatin as a subsequent therapy. "Completed induction phase" indicates that a patient completed the induction phase without entering a maintenance phase.

the primary database lock (August 27, 2010), three patients in the concurrent ipilimumab arm, two patients in the phased ipilimumab arm, and one patient in the control arm were still on treatment. The primary reason for treatment discontinuation was disease progression. Baseline demographics and disease characteristics were generally balanced across arms with the exceptions that the control arm had fewer patients with stage IV disease (control arm, 74% of patients; concurrent arm, 84% of patients; phased arm, 90% of patients), and the phased ipilimumab arm had a higher percentage of patients with a Eastern Cooperative Oncology Group performance status of 0 compared with the control arm (37% *v* 23%, respectively; Table 1).

The median number of ipilimumab doses during the entire treatment period (induction plus maintenance) was four in both the concurrent ipilimumab arm (range, one to 12 doses) and phased ipilimumab arm (range, one to 11 doses). Twenty-one patients (30%) in the concurrent ipilimumab arm and 23 patients (34%) in the phased ipilimumab arm received five or more doses of ipilimumab. Median numbers of paclitaxel and carboplatin doses in the control, concurrent ipilimumab, and phased ipilimumab arms were six, four, and five, respectively (range, one to six doses in all arms). The number of patients who entered the maintenance phase was 25 patients (38%) in the control arm, 23 patients (32%) in the concurrent ipilimumab arm, and 24 patients (36%) in the phased ipilimumab arm. The median number of ipilimumab doses in the maintenance phase was two for both the concurrent ipilimumab (range, one to eight doses) and phased ipilimumab (range, one to seven doses) arms, and the median number of placebo doses in the control arm was one (range, one to seven doses).

Table 1. Baseline Patient Demographics and Disease Characteristics

Demographic or Disease Characteristic	Control (n = 66)* No. of Patients	%	Concurrent Ipilimumab (n = 70)† No. of Patients	%	Phased Ipilimumab (n = 68)‡ No. of Patients	%
Age, years						
Median	62		59		61	
Range	36-82		36-82		36-88	
Sex						
M	49	74	53	76	49	72
F	17	26	17	24	19	28
Ethnicity						
White	54	82	58	83	56	82
Asian	10	15	10	14	10	15
Black/African American	2	3	1	1	2	3
Hispanic	0		1	1	0	
ECOG performance status						
0	15	23	19	27	25	37
1	51	77	51	73	43	63
Tumor histology						
Adenocarcinoma	38	58	35	50	30	44
Squamous-cell carcinoma	15	23	21	30	21	31
Large-cell carcinoma	7	11	6	9	11	16
Bronchoalveolar carcinoma	0		1	1	1	1
Other	3	5	6	9	4	6
Unknown	3	5	1	1	1	1
Disease stage						
IIIB	17	26	11	16	7	10
IV	49	74	59	84	61	90
Serum lactate dehydrogenase level						
> Upper limit of the normal range	17	26	26	37	21	31

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Placebo plus paclitaxel and carboplatin.
†Ipilimumab plus paclitaxel and carboplatin followed by placebo plus paclitaxel and carboplatin.
‡Placebo plus paclitaxel and carboplatin followed by ipilimumab plus paclitaxel and carboplatin

Efficacy

Progression data used for the analysis of primary end point of irPFS were obtained by using the irRC criteria (Patients and Methods). The phased ipilimumab regimen improved irPFS significantly compared with the control regimen (HR, 0.72; $P = .05$; Fig 2), whereas the concurrent ipilimumab regimen did not significantly improve irPFS (HR, 0.81; $P = .13$). The median irPFS was 4.6 months for the control regimen, 5.7 months for the phased

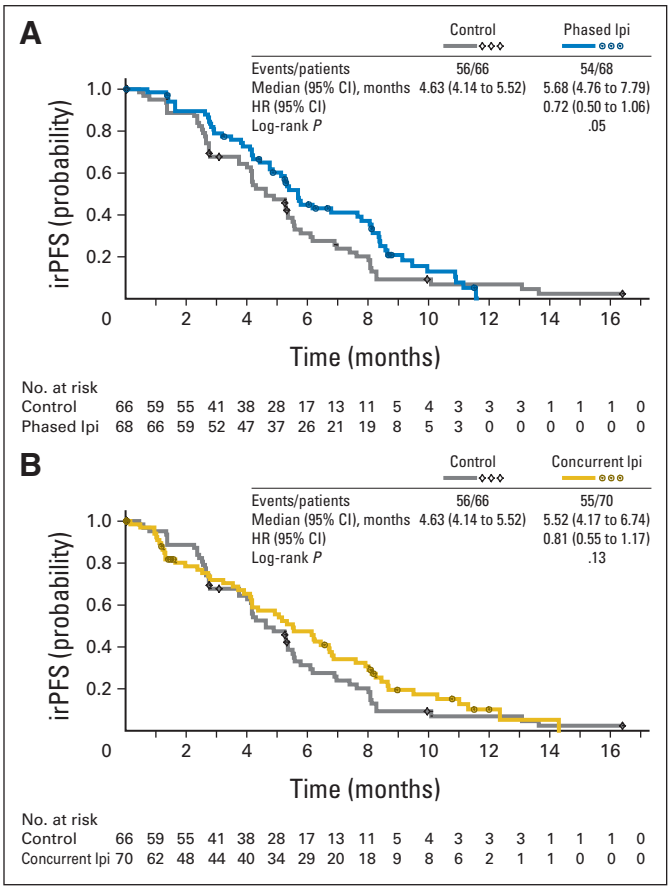

Fig 2. Kaplan-Meier plots for progression-free survival per immune-related response criteria (irPFS). To account for the unique tumor-response patterns to ipilimumab (Ipi), immune-related response criteria (irRC) were proposed. Per irRC, new lesions, whether measurable or not, were not considered a progression. Instead, measurable new lesions were added to index lesions to obtain a total tumor burden, and a ≥ 25% reduction in this tumor burden from nadir was defined as immune-related progression. irPFS was defined as the time from random assignment to immune-related progression (as determined by an independent radiologic review committee) or death. As indicated by symbols, patients who neither progressed nor died were censored on the date of the last tumor assessment. *P* values were based on an unstratified log-rank test with a one-sided α of 0.1. HR, hazard ratio. (A) Control *v* phased Ipi; (B) control *v* concurrent Ipi.

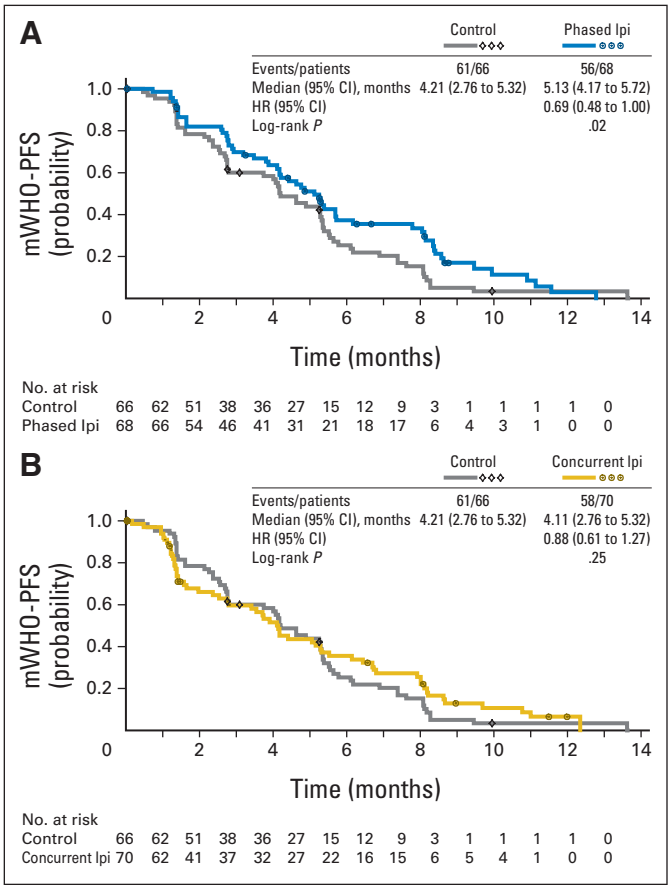

Fig 3. Kaplan-Meier Plots for progression-free survival per modified WHO criteria (mWHO-PFS). Per modified WHO criteria (mWHO), a reduction in index lesions by ≥ 25% or any new lesions (measurable or not) or a progression of nonindex lesions were considered an mWHO progression. mWHO-PFS was defined as the time from random assignment to mWHO progression (as determined by an independent radiologic review committee) or death. As indicated by symbols, patients who neither progressed nor died were censored on the date of last tumor assessment. *P* values were based on an unstratified log-rank test with a one-sided α of 0.1. HR, hazard ratio; Ipi, ipilimumab. (A) Control *v* phased Ipi; (B) control *v* concurrent Ipi.

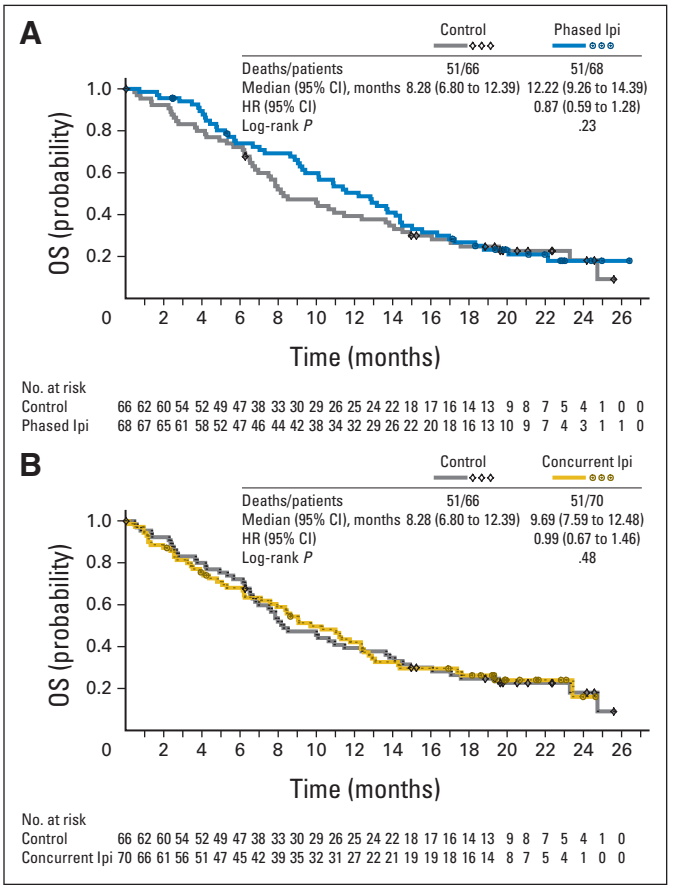

Fig 4. Kaplan-Meier plots for overall survival (OS). OS was defined as the time from random assignment until death as a result of any cause. As indicated by symbols, patients who had not died or who were lost to follow-up were censored on the last date on which they were known to have been alive. *P* values were based on an unstratified log-rank test with a one-sided α of 0.1. HR, hazard ratio; Ipi, ipilimumab. (A) Control *v* phased Ipi; (B) control *v* concurrent Ipi.

ipilimumab regimen, and 5.5 months for the concurrent ipilimumab regimen. As assessed by using the mWHO criteria, there was also an improvement in PFS, relative to the control, for phased ipilimumab (HR, 0.69; $P = .02$; Fig 3) but not for concurrent ipilimumab (HR, 0.88; $P = .25$). The median mWHO-PFS was 4.2 months for the control group, 5.1 months for the phased ipilimumab group, and 4.1 months for the concurrent ipilimumab group.

The median OS for the phased ipilimumab group was 12.2 months, which was an increase of 3.9 months over the median of 8.3 months for the control group (HR, 0.87; $P = .23$; Fig 4). The median OS of 9.7 months for the concurrent ipilimumab group was similar to that of the control group (HR, 0.99; $P = .48$; Fig 4). Rates of OS for concurrent ipilimumab, phased ipilimumab, and control group were 42%, 50%, and 39%, respectively, at 1 year and 16%, 18%, and 18%, respectively, at 2 years.

To determine whether any pretreatment characteristics predicted for clinical outcome, we performed subset analyses for irPFS, mWHO-PFS, and OS on the basis of age, sex, performance status, disease stage, and histology. Although the numbers of patients in the subsets were small, none of these baseline factors had an apparent impact on irPFS or mWHO-PFS, with the exception of histology. In the phased ipilimumab arm, improvements in irPFS versus those in the control arm appeared to be greater in patients with squamous histology (HR, 0.55 [95% CI, 0.27 to 1.12]) than in patients with nonsquamous histology (HR, 0.82 [95% CI, 0.52 to 1.28]). In the phased ipilimumab arm, mWHO-PFS also favored the squamous subset (HR, 0.40 [95% CI, 0.18 to 0.87]) over the nonsquamous subset (HR, 0.81 [95% CI, 0.53 to 1.26]). However, in the concurrent ipilimumab arm, differences in irPFS versus that in the control arm were similar between squamous and nonsquamous subsets (HR, 0.85 [95% CI, 0.42 to 1.74] and 0.77 [95% CI, 0.49 to 1.20], respectively) as were differences in mWHO-PFS (HR, 0.87 [95% CI, 0.42 to 1.81] and 0.88 [95% CI, 0.57 to 1.35], respectively). In the phased ipilimumab arm, HR values for OS versus those in the control arms were 0.48 (95% CI, 0.22 to 1.03) for the squamous subset and 1.17 (95% CI, 0.74 to 1.86) for the nonsquamous subset; corresponding HR values in the concurrent ipilimumab arm were 1.02 (95% CI, 0.50 to 2.08) and 0.96 (95% CI, 0.60 to 1.53), respectively.

irBORR and mWHO-BORR, as determined on the basis of assessment by blinded independent radiologic review committee were

both 21% for concurrent ipilimumab and 32% for phased ipilimumab arms (Table 2). irBORR and mWHO-BORR for the control regimen were 18% and 14%, respectively. irDCR was 82% for the control regimen, 70% for the concurrent ipilimumab regimen, and 87% for the phased ipilimumab regimen. Corresponding mWHO-DCRs were 73%, 57%, and 78%, respectively.

Safety

As shown in Table 3, the overall incidence of treatment-related grade 3 and 4 AEs was similar across arms (control, 37%; concurrent, 41%; phased, 39%). The most common nonhematologic AEs (≥15%, any grade) typically associated with paclitaxel and carboplatin, including fatigue, alopecia, nausea, vomiting, and peripheral sensory neuropathy, were generally similar across arms. Other common AEs, such as rash, pruritus, and diarrhea, showed a trend for increased incidence in the ipilimumab-containing arms than in paclitaxel and carboplatin arms, and these AEs were also identified as irAEs per protocol-defined criteria. Hematologic abnormalities were generally similar across arms.

The most common AEs were mostly grade 1 and 2 events; there were no grade 4 events except for one grade 4 case of fatigue in the concurrent ipilimumab arm (Table 3). The overall incidence of grade 3 and 4 irAEs was 6% for the control arm, 20% for the concurrent ipilimumab arm, and 15% for the phased ipilimumab arm. Two patients who received concurrent ipilimumab, two patients who received phased ipilimumab, and one patient who received the control regimen had a grade 3 rash. Grade 3 diarrhea was reported in five patients who received concurrent ipilimumab, three patients who received phased ipilimumab, and two patients who received the control regimen. Two cases of grade 3 colitis were noted in the phased ipilimumab arm. One patient in each arm reported grade 3 increases in liver-function enzymes. One case each of grade 3 hypophysitis and hypopituitarism was reported in the concurrent ipilimumab arm.

There were two events of grade 3 hypersensitivity reaction in the concurrent ipilimumab arm, one grade 4 event in the phased ipilimumab arm, and one grade 3 event in the control arm. One grade 4 event each of pulmonary embolism, dyspnoea, and anaphylactic reaction occurred in the concurrent ipilimumab arm, one grade 4 event of pulmonary embolism occurred in the phased ipilimumab arm, and one grade 3 event of dyspnoea occurred in the control arm.

Drug-related toxicity was the cause of treatment discontinuation for three patients (5%) who received the control regimen, seven patients (10%) who received the concurrent ipilimumab regimen, and four patients (6%) who received the phased ipilimumab regimen. Two deaths were reported to be treatment related (one death occurred in the concurrent ipilimumab arm as a result of septic shock secondary to epidermal necrolysis, and one death occurred in the control arm as a result of neutropenic sepsis).

Table 2. Tumor Response and Disease Control

	Control (n = 66)		Concurrent Ipilimumab (n = 70)		Phased Ipilimumab (n = 68)	
Response	No. of Patients	%	No. of Patients	%	No. of Patients	%
irBOR						
irCR	0		0		0	
irPR	12	18	15	21	22	32
irSD	42	64	34	49	37	54
irPD	2	3	6	9	5	7
Unknown	10	15	15	21	4	6
irBORR						
%	18		21		32	
95% CI	10 to 30		13 to 33		22 to 45	
irDCR						
%	82		70		87	
95% CI	70 to 90		58 to 80		76 to 94	
mWHO-BOR						
CR	0		0		0	
PR	9	14	15	21	22	32
SD	39	59	25	36	31	46
PD	11	17	16	23	11	16
Unknown	7	11	14	20	4	6
mWHO-BORR						
%	14		21		32	
95% CI	6 to 24		13 to 33		22 to 45	
mWHO-DCR						
%	73		57		78	
95% CI	60 to 83		45 to 69		66 to 87	

Abbreviations: CR, complete response; irBOR, immune-related best overall response; irBORR, immune-related best overall response rate; irCR, immune-related complete response; irDCR, immune-related disease control rate; irPD, immune-related progressive disease; irPR, immune-related partial response; irSD, immune-related stable disease, mWHO-BOR, modified WHO best overall response; mWHO-BORR, modified WHO best overall response rate; mWHO-DCR, modified WHO disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

DISCUSSION

This study of ipilimumab in patients with previously untreated NSCLC met its primary end point of improved irPFS for the phased ipilimumab regimen (HR, 0.72; $P = .05$) but not for the concurrent ipilimumab regimen (HR, 0.81; $P = .13$) compared with paclitaxel and carboplatin alone. Phased ipilimumab, but not concurrent ipilimumab, also improved mWHO-PFS. The median OS of 12.2 months for in the phased ipilimumab arm was similar to that reported for the combination of paclitaxel and carboplatin with bevacizumab (12.3 months).[3] The current phase II results suggested an improved efficacy of ipilimumab in patients with previously untreated NSCLC when combined with paclitaxel and carboplatin as a phased, but not concurrent, regimen. Phased ipilimumab provided chemotherapy exposure before ipilimumab administration, and this may potentially have contributed to the enhanced activation of T cells.[33-35]

Results of this phase II study were consistent with recent findings in patients with NSCLC by using other immunotherapy approaches. Several studies in patients with NSCLC suggested an association of increased tumor infiltration of immune cells with improved survival.[47-52] In addition, phase II studies that evaluated vaccination strategies such as melanoma-associated antigen-A3 (MAGE-A3; GlaxoSmithKline Biologicals, Rixensart, Belgium) and Biomira liposomal protein 25 (BLP25; Oncothyreon, Seattle, WA) vaccines reported trends for improved efficacy in patients with NSCLC.[53-55]

Histology is emerging as a factor in selecting agents for NSCLC treatment, as suggested by the fact that bevacizumab and pemetrexed are approved treatments for nonsquamous NSCLC but not for squamous NSCLC.[56,57] In this trial, phased ipilimumab appeared to show improved efficacy for squamous histology, but there was no apparent

Table 3. Adverse Events

Event	Control (n = 65)			Concurrent Ipilimumab (n = 71)			Phased Ipilimumab (n = 67)		
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4
Any adverse event, %	31	29	11	16	30	27	19	42	12
Any treatment-related adverse event, %	43	29	8	35	24	17	43	31	8
Treatment-related non-hematologic adverse events, %									
Fatigue	22	5	0	20	7	1	19	5	0
Alopecia	46	NA	NA	34	NA	NA	45	NA	NA
Rash	8	2	0	25	3	0	10	3	0
Pruritus	5	2	0	17	0	0	8	0	0
Arthralgia	11	0	0	16	0	0	12	2	0
Asthenia	3	2	0	4	3	0	16	2	0
Diarrhea	14	3	0	23	7	0	18	5	0
Nausea	31	2	0	25	1	0	31	2	0
Vomiting	15	2	0	17	1	0	16	2	0
Peripheral neuropathy*	23	2	0	13	1	0	10	0	0
Peripheral sensory neuropathy*	11	2	0	8	0	0	16	3	0
Hematologic abnormalities, %†									
Thrombocytopenia	35	8	2	39	2	0	40	3	0
Neutropenia	32	8	2	26	5	3	34	2	0
Anemia	89	6	0	80	8	3	92	6	0
Liver-function enzymes, %†									
ALT	35	2	0	40	2	0	29	2	0
AST	32	2	0	25	2	0	31	2	0

NOTE. Adverse events listed were those (any grade) reported in ≥15% of patients in any arm. Patients could have more than one adverse event.
Abbreviation: NA, not applicable.
*As reported by investigators (standardized Medical Dictionary for Regulatory Activities query term scope).
†On the basis of laboratory results.

benefit for nonsquamous histology. Although caution is warranted in interpreting these subset data from a small phase II study, it is notable that tumor-infiltrating T cells are more abundant in squamous NSCLC.[48,51,58] Additional trials in conjunction with translational research are needed to confirm our findings in patients with squamous NSCLC.

To our knowledge, this was the first prospective randomized study that used irRC as preplanned criteria for response assessments. Response rates per irRC were generally similar to those per mWHO criteria. However, 11 patients who had PD (mWHO) without irPD were not assessed for a tumor response beyond PD, which resulted in an incomplete assessment of immune-related responses.

The most common AEs involving skin and gastrointestinal tract (eg, rash, pruritus, and diarrhea) were also identified as irAEs according to protocol-defined criteria. Consistent with previous experience from other studies, these irAEs occurred more frequently in arms that contained ipilimumab and were mostly grades 1 and 2. The use of corticosteroids as premedication for paclitaxel could have attenuated the severity of irAEs. Most irAEs of clinical relevance in this trial were managed by protocol-specified treatment guidelines, including close patient follow-up and the early administration of systemic corticosteroids.[26,59] Hematologic abnormalities were generally similar across arms as were common nonhematologic AEs typically associated with paclitaxel and carboplatin.

In conclusion, in previously untreated patients with NSCLC, the combination of ipilimumab with paclitaxel and carboplatin as a phased, but not as a concurrent, regimen significantly improved irPFS and mWHO-PFS. There was no apparent impact of ipilimumab on toxicities seen with paclitaxel and carboplatin alone, and the pattern of irAEs was consistent with data from published ipilimumab studies. Similar findings were reported for the cohort with ED-SCLC in this trial.[40] Taken together, these results provide justification for additional investigation of ipilimumab in combination with chemotherapy in patients with NSCLC. Results in patients with squamous NSCLC warrant further exploration in a larger clinical trial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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