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ORIGINAL REPORT

Randomized Phase II Trial of Paclitaxel Plus Carboplatin or Gemcitabine Plus Cisplatin in Eastern Cooperative Oncology Group Performance Status 2 Non–Small-Cell Lung Cancer Patients: ECOG 1599

Corey Langer, Sigui Li, Joan Schiller, William Tester, Bernardo L. Rapoport, and David H. Johnson

From the Fox Chase Cancer Center; Albert Einstein Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; University of Wisconsin Cancer Center, Madison, WI; Mayo Clinic, Rochester, MN; and Vanderbilt University, Nashville, TN.

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Address reprint requests to Corey J. Langer, MD, FACP, Thoracic Oncology, Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA 19111; e-mail: cj_langer@fccc.edu

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ABSTRACT

Purpose
Appropriate therapy for Eastern Cooperative Oncology Group (ECOG) performance status (PS) -2 patients with advanced non–small-cell lung cancer (NSCLC) remains challenging. PS-2 patients on ECOG 1594 had a median survival (MS) of only 4.1 months and 1-year overall survival (OS) of 19%. Three percent had grade 5 toxicity.

Patients and Methods
ECOG 1599, the first PS 2–specific, US cooperative group trial for treatment-naïve advanced NSCLC, randomly assigned patients to dose-attenuated carboplatin/paclitaxel (the least toxic regimen in ECOG 1594) or gemcitabine/cisplatin (which yielded an MS of 7.9 months in PS-2 patients). Patients received either carboplatin (area under the concentration-time curve, 6) and paclitaxel 200 mg/m^2 every 3 weeks (CbP) or gemcitabine 1 g/m^2 days 1 and 8 and cisplatin 60 mg/m^2 day 1 every 3 weeks (CG).

Results
One hundred three patients were enrolled; 100 proved eligible. Median age was 66 years; 46% had at least 5% weight loss; 88% had stage IV or recurrent disease. Median number of cycles administered was three per arm. CbP featured more grade 3 neutropathy (10% *v* 0%) and more grade ≥ 3 neutropenia (59% *v* 33%), whereas CG yielded more grade ≥ 3 thrombocytopenia (33% *v* 14%), more grade ≥ 3 fatigue (22% *v* 14%), and more grade ≥ 1 creatinine elevations (43% *v* 6%). One grade 5 toxicity, confined to the CbP arm, occurred. Response rate, time to progression, MS, and 1-year OS rates for CG and CbP, were 23%, 4.8 months, 6.9 months, and 25%, and 14%, 4.2 months, 6.2 months, and 19%, respectively.

Conclusion
Platinum-based combination chemotherapy for PS-2 patients with NSCLC is feasible with acceptable toxicity, but survival in these patients remains inferior to that of PS-0 to -1 patients.

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INTRODUCTION

Performance status (PS) is a critical prognostic factor in advanced non–small-cell lung cancer (NSCLC). In the 1980s and 1990s, clinical trials and retrospective analyses suggested that patients with advanced NSCLC and compromised PS experienced substantial toxicity, gaining virtually no benefit from systemic chemotherapy.[1-8] A 1986 Eastern Cooperative Oncology Group (ECOG) trial was one of the first to demonstrate impaired outcome for PS-2 patients.[9] Four hundred eighty-six patients were randomly assigned over 2 years among four platinum-based combinations. Nineteen percent had PS 2, defined as symptomatic from disease and spending less than 50% of waking hours in bed. Median survival (MS) for PS-0 and PS-1 patients was 36 and 26 weeks, respectively, but it was only 10 weeks for PS-2 patients.[9] PS-2 patients also sustained 10% incidence of treatment-related deaths, substantially higher than the incidence in PS-0 to -1 patients. Consequently, PS-2 patients were excluded from subsequent ECOG NSCLC trials.

By the mid-1990s, improved supportive therapy (antiemetics, growth factors, and antibiotic management for myelosuppression) and somewhat less toxic active agents permitted ECOG investigators to enroll PS-2 patients onto 1594, a randomized, phase III, prospective trial evaluating four separate platinum-based regimens.[10] More than

1,200 patients were ultimately accrued to 1594. However, after the first 68 patients, accrual of the PS-2 cohort was halted due to a high incidence of adverse events, including five deaths. A subsequent analysis showed that only two of the five were clearly treatment related.[11] Nevertheless, toxicity was perceived as worse for this group compared with patients with PS 0 to 1. Further analysis showed that toxicity was only marginally worse. The overall response rate for PS-2 patients was only 14%, with MS 4.1 months and a 1-year overall survival (OS) rate of 19.1%. The gemcitabine/cisplatin (CG) arm, despite the greatest toxicity, yielded the best MS and 1-year OS in this group: 7.9 months and 38.5%. The carboplatin/paclitaxel (CbP) arm featured the least toxicity. Based on these findings, we proceeded with a PS-2–specific trial in advanced NSCLC, evaluating dose-attenuated versions of both regimens for feasibility and activity in PS-2 patients with incurable NSCLC.

PATIENTS AND METHODS

The primary objective was an assessment of overall survival for each regimen in PS-2 NSCLC; secondarily, evaluation of response rate, time to progression, and toxicities.

Eligibility stipulated advanced, incurable, chemotherapy-naïve NSCLC; ECOG PS 2; age at least 18 years; adequate physiologic indices, including absolute neutrophil count of at least 2,000; platelets at least 100,000; creatinine 1.5 mg/dL or lower; bilirubin 1.5 mg/dL or lower; and signed informed consent.

Patients were deemed ineligible if they had received prior radiation to assessable disease (unless disease progression was confirmed at that site by physical examination, radiography, or pathology) or had pre-existing grade 2 or higher sensory neuropathy, CNS metastases untreated or actively growing despite prior radiation or surgery, or other active concurrent malignancies. Patients were also excluded for pregnancy, allergies to polyoxyethylate castor oil and significant comorbidities precluding chemotherapy, including active congestive heart failure and recent myocardial infarction.

Protocol Treatment

At study entry, patients were randomly assigned to arm A or B using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Stratification factors included weight loss in preceding 6 months ($< 5\%$ *v* $\geq 5\%$) and disease stage (stage IIIb with pleural or pericardial effusion by computed tomography [CT] or chest x-ray [CXR] or pleural implants documented pathologically, on CT or CXR *v* stage IV/recurrent).

On arm A (CbP), patients received 200 mg/m^2 paclitaxel intravenously (IV) day 1 over 3 hours. Carboplatin was administered at a dose targeting an area under the concentration-time curve (AUC) of 6, over 30 minutes immediately after paclitaxel. Before paclitaxel, all patients received routine premedication including dexamethasone, diphenhydramine (or equivalent), and cimetidine (or other H2 blockers). Treatment was cycled at 3-week intervals, including standard antiemetic prophylaxis.

Patients enrolled onto arm B (CG) received gemcitabine 1,000 mg/m^2 IV over 30 minutes on days 1 and 8 and cisplatin 60 mg/m2 IV day 1 over 1 hour. Cycles were repeated every 3 weeks. Routine prehydration and aggressive antiemetics preceded cisplatin.

Standard ECOG response criteria were used. Patients with complete response (CR), partial response (PR), or stable disease were allowed to continue treatment for up to six cycles, or until disease progression or unacceptable toxicity. Criteria for treatment cessation included progressive disease, excessive toxicity, patient choice, or intercurrent comorbidities.

Statistical Methods

The primary end point of this trial was 1-year OS. The trial was designed to detect an absolute 10% increase in 1-year OS compared with historic controls. The 1-year OS rate of PS-2 patients enrolled onto ECOG 1594 was roughly 20%. Therefore, using Simon et al's 1995 statistical selection criterion, the treatment demonstrating superior 1-year OS would be studied further.[7] The sample size was determined to ensure that if 1-year OS for one treatment was superior by at least 10%, it would be selected with high probability. This study design had an 86% chance of selecting a treatment yielding 1-year OS of at least 30%, assuming a rate of 20% for the historic control or alternative arm. Sample size based on these calculations stipulated a minimum of 45 patients per arm. Assuming that 10% proved unassessable, 99 patients were projected for accrual.

Because of overriding concern about severe toxicity in this vulnerable population, a two-stage design was independently applied to each arm so that symptomatic treatment-related grade 4 or 5 toxicity, excluding transient, asymptomatic hematologic toxicity in either regimen, would result in termination of that arm. The trial was designed to halt a particular regimen if more than eight instances of such toxicities occurred among the first 20 patients enrolled. This design necessitated a mandatory interim stopping period for toxicity analysis. Descriptive statistics were used to describe patient characteristics on study.

OS and progression-free survival (PFS) were estimated by the Kaplan-Meier method.[4] CIs for toxicity rate were estimated using exact binomial CIs adjusted for two-stage design.[5] These were calculated for overall response rate and 1-year OS rates.[6] All reported *P* values were associated with two-sided tests, unless otherwise specified.

RESULTS

Patient Demographics

One hundred three patients were accrued (54 in arm A, 49 in arm B) between May 31, 2000, and November 20, 2002. The study underwent mandatory suspension on May 8, 2001, and, in the absence of unacceptable toxicity, was reopened on November 27, 2001.

One patient deemed ineligible had stage IIIb disease without pleural effusion. Four eligible patients also never started protocol therapy. Two experienced rapid decline in performance status; a third required emergency treatment for ventricular arrhythmia; a fourth died as a result of cardiopulmonary arrest before treatment was initiated.

Baseline demographics were comparable for both arms (Table 1). Median age was 66 years. Sixty-five percent were male; 46% had at least 5% weight loss. Eighty-eight percent had stage IV or recurrent disease. A slightly higher proportion of men were enrolled on the CG arm (71% *v* 59%). The CbP arm had a higher proportion of stage IIIb patients (19% *v* 10%). These differences were not statistically significant. Twenty percent of patients had squamous histology.

Toxicity

Of 51 patients receiving CbP, 27% completed all six cycles of therapy, 11% received more than six cycles, and 49% received at least four. The median number of treatment cycles for both arms was three. Of 47 treated patients receiving CG, 31% completed all six cycles, 10% received more than six cycles, and 46% received at least four.

Toxicity is summarized in Table 2. One patient in arm A had lethal toxicity (grade 5 febrile neutropenia). The CbP arm featured substantially more grade 3 or higher neutropenia than did the CG arm (59% *v* 33%); the relative incidence of grade 4 neutropenia was 34% and 10%, respectively. CbP also featured significantly more grade 3 sensory neuropathy (10% *v* 0%) and grade 2 sensory neuropathy (16% *v* 2%). However, CG resulted in significantly more grade 3 or higher thrombocytopenia (38% *v* 14%). It yielded significantly more grade 3 nausea/vomiting (23% *v* 6%), grade 3 fatigue (22% *v* 12%), and grade 1 or higher creatinine elevation (43% *v* 6%).

Table 1. Arm-Specific Demographics

Characteristic	CG	CbP
Age, years		
Median	67	65
Range	42-81	45-80
Sex, %		
Male	59	74
Female	41	26
≥ 5% weight loss, %	47	40
Stage		
IIIB	18	9
IV	73	79
Recurrent	10	13
Histology		
Squamous	21	18
Adenocarcinoma	45	51
Not otherwise specified	34	31
Race/ethnicity		
White	73	80
African American	22	18
Other	6	2
Prior RT	18	40

Abbreviations: CbP, carboplatin/paclitaxel; GC, gemcitabine/cisplatin; RT, radiotherapy.

Treatment Discontinuation

The most common reason for treatment discontinuation was progressive disease (49% in arm A, 40% in arm B; Table 3). Excess toxicity precipitated treatment suspension for 16% in arm A and 15% in arm B, whereas other reasons were more common in the cisplatin-based arm (13% *v* 4%). Comorbidities that were unrelated to treatment resulted in treatment suspension for 4% in arm A and 9% in arm B.

Objective Responses

The overall objective response rate for arm B was 23% (90% CI, 13.1 to 34.4), including 1 CR. For arm A, it was 14% (90% CI, 6.4 to 23.4). Median response duration for patients on arms A and B were 5.3 and 6.5 months, respectively. Grouping stable disease and response together, arm A featured disease control rates of 55% versus 53% for arm B. Objective responses are show in Table 4.

Table 2. Maximum Toxicity

	CbP		GC	
	Grade 3	Grade 4	Grade 3	Grade 4
No. assessable % toxicity	51		47	
Neutropenia	25	34	23	10
Thrombocytopenia	12	0	33	5
Anemia	10		13	
Nausea/vomiting	6	0	23	0
Sensory neuropathy	10		0	
Fatigue	12	2	22	0
Creatinine grade ≥ 1	6		43	
Worst grade	43	37	57	23

Abbreviations: CbP, carboplatin/paclitaxel; GC, gemcitabine/cisplatin.

Table 3. Reasons for Treatment Discontinuation

Reason	CbP		GC	
	No.	%	No.	%
Treatment completed	9	18	10	21
Progressive disease	25	49	19	40
Excessive complication	8	16	7	15
Death without progression	1	2	0	0
Patient withdrawal	2	4	6	13
Other complicating disease	2	4	4	9
Other	4	8	1	2
Total	51	100	47	100

Abbreviations: CbP, carboplatin/paclitaxel; GC, gemcitabine/cisplatin.

Survival Data

PFS was defined as time from random assignment to tumor progression or death without documented disease progression (Fig 1). Kaplan-Meier estimate of PFS for CbP was 3.5 months (95% CI, 2.6 to 6.0), and 3.0 months for CG arm (95% CI, 1.7 to 4.8). Survival data are show in Table 4.

OS was defined as time from random assignment to death or last contact. Figure 2 displays Kaplan-Meier estimate of OS by treatment arm. MS was 6.9 months for the CG arm, with 1-year OS of 25.5% (95% CI, 13.1 to 38.0) and a 2-year survival rate of 13% (95% CI, 3.3 to 22.0). MS for CbP was 6.2 months, with 1-year OS of 19.6% (95% CI, 8.7 to 30.5) and a 2-year survival rate of 7.8% (95% CI, 0.5 to 15.2).

As of this report (May 2005), two patients (4%) in the CbP arm remained alive, whereas three patients (6%) in the CG arm survived. The study was not designed to compare 1-year OS in the two treatment groups at the usual .05 level. Given the original design of the study, we had only 20% power to detect an absolute 10% improvement in 1-year OS, assuming the 1-year OS in one arm was 20%.

DISCUSSION

Although the assignment of PS is a subjective phenomenon, open to both questions and debate, we have long recognized that impaired PS is associated with compromised survival in patients with advanced NSCLC. A retrospective recursive partitioning analysis of multiple ECOG studies through the 1980s and early 1990s showed that performance status, sex, and appetite (and, by inference, weight loss)

Table 4. Therapeutic Outcome

Outcome	CG	CbP
OR, %	23	14
OR/SD, %	53	55
TTP, months	4.8	4.2
PFS, months	3.0	3.5
MS, months	6.9	6.2
1-year OS, %	25	19

Abbreviations: CbP, carboplatin/paclitaxel; GC, gemcitabine/cisplatin; OR, objective response; SD, stable disease; TTP, time to progression; PFS, progression-free survival; MS, median survival; OS, overall survival.

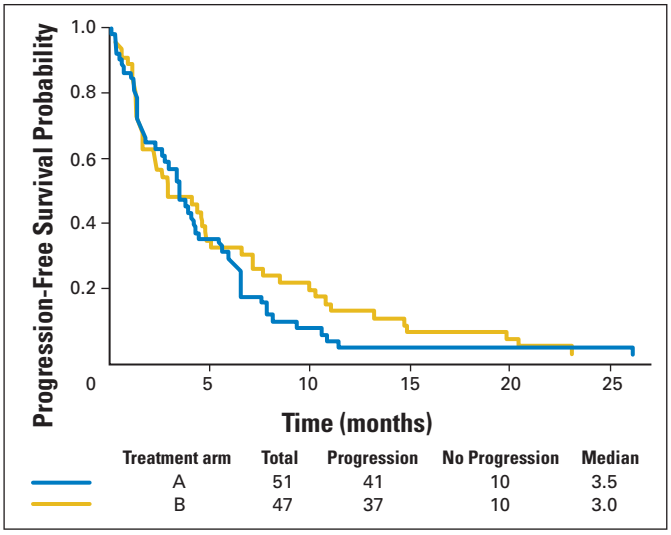

Fig 1. Progression-free survival by treatment. Prog, progression.

were the three most important prognostic factors. These prognostic indices relate directly to the intrinsic biology of the tumor and the patient, both of which may be inextricably linked.

Historically, PS-2 patients with advanced NSCLC have fared poorly. In a phase III trial by Alberola et al[12] comparing gemcitabine/cisplatin to triplet therapy (cisplatin/gemcitabine/vinorelbine), as well as sequential nonplatinum doublets (gemcitabine/vinorelbine ifosfamide/vinorelbine), PS-2 individuals had an MS of only 4.8 months, compared with 9.1 months for PS 0 to 1. van Meerbeeck et al[13] mounted a phase III trial comparing cisplatin combinations with either paclitaxel or gemcitabine compared with the nonplatinum constituents (paclitaxel/gemcitabine), with no significant long-term survival difference among the three arms. However, MS in the PS-2 cohort was only 3.3 months, compared with 8.6 months for PS 0 to 1. In a phase III trial pairing carboplatin (AUC, 6) with paclitaxel at either low dose (175 mg/m^2) or high dose (225 mg/m^2), Kosimidis[14]

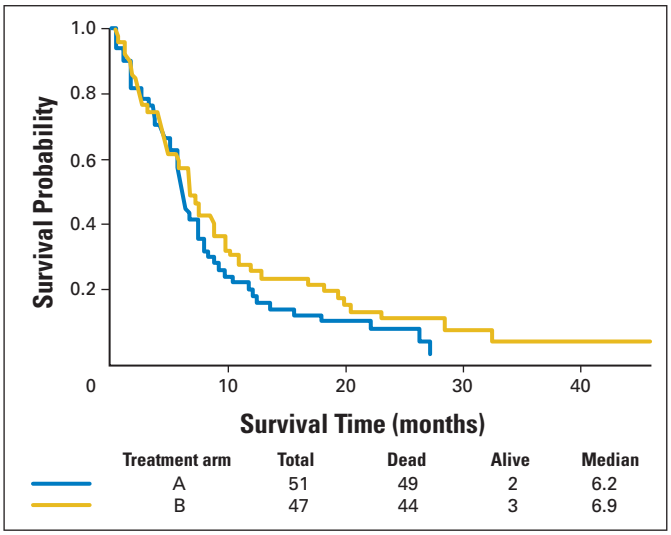

Fig 2. Overall survival by treatment.

showed similar striking differences based on PS: MS in the PS-2 cohort was 3.8 months compared with 11.5 months for PS 0 to 1.

ECOG 1599 is the first United States PS-2–specific trial ever conducted in treatment-naïve advanced NSCLC. The results demonstrate that combination platinum-based therapy is feasible in this group. With appropriate attenuation of initial paclitaxel, gemcitabine, and platinum doses, toxicities essentially matched those observed historically in the PS-0 to -1 population.

Paclitaxel/carboplatin yielded more sensory neuropathy and neutropenia, but less nausea/vomiting, thrombocytopenia, and fatigue, and fewer creatinine elevations compared with gemcitabine/cisplatin. Disease control rates were comparable. MS exceeded 6 months for each regimen, somewhat better than the historic control of 4 months or less previously observed in ECOG trials,[9-11,15] and as such constitutes a reasonable benchmark for future research. Still, 1-year OS did not exceed 30% in either arm.

There were no statistically significant differences in survival between the two arms. The 1% grade 5 adverse event rate, in the context of a multi-institutional cooperative group trial, was acceptable.

With regard to this study, we must acknowledge several concerns. Potential imbalances exist in the baseline demographics of each arm. The GC arm had fewer women, more patients who underwent prior radiotherapy, and fewer patients with stage III disease. Hence, it is conceivable that outcome might have been considerably better in this arm had baseline demographics been completely identical. But it is still doubtful that 1-year OS would exceed 30%. In addition, we did not establish baseline quality of life (QoL) or compare QoL between arms; this sort of comparison, however, is generally the province of phase III trials, and probably has more important implications in studies where the nature of therapeutic interventions are more disparate.

A number of additional issues remain outstanding. We recognize that the assignment of PS is subjective, and open to both questions and debate. In the context of ECOG trials, the assignment of PS was based on physician designation, although nursing viewpoints may have helped inform this designation. From the standpoint of study entry, PS can only be assigned at baseline. We readily recognize that QoL, both at baseline and during the course of study, may depend on supportive care interventions, not necessarily response status, and we must acknowledge the potential palliative role of radiation in PS-2 patients.

We need to better understand reasons for compromised PS (ie, comorbidity *v* disease burden *v* both), and determine the extent to which each influences outcome. In addition, a standard of treatment in this population must be established. Should PS-2 patients receive combination therapy, or should single agents with improved toxicity profile be pursued sequentially? It is conceivable that chemotherapy can potentially exacerbate the clinical situation in patients who are relatively asymptomatic from the cancer itself, but highly symptomatic from the comorbidities, whereas those patients whose poor PS is due to cancer burden may actually benefit far more from treatment. Unfortunately, ECOG 1599 did not provide comprehensive data on preexisting comorbidity, compromising our capacity to distinguish outcome based on disease burden versus pre-existing illnesses. In a Southern Italian Cooperative Oncology Group trial by Frasci et al[16] focusing on elderly patients, baseline Charlson score (comorbidity index) correlated with both treatment completion rates and MS. Eighty-two percent of those with Charlson scores higher than 2

stopped treatment early, compared with a 30% early treatment-discontinuation rate among those with Charlson scores of 0 to 2. Those with Charlson score 0 had an MS of 6.5 versus 4.8 months for Charlson scores 1 to 2, whereas the MS of those with Charlson scores higher than 2 was 3.7 months. Similarly, in the MILES (Multi-Center Italian Lung Elderly Study) effort comparing gemcitabine/vinorelbine with the constituent single agents, baseline instrumental activities of daily living and QoL predicted outcome.[17] Had sufficient data been collected on ECOG 1599, a similar determination could have been accomplished.

To date, we still lack PS-2-specific studies directly comparing platinum-based doublets to either platinum alone or to the nonplatinum partner. Lilienbaum et al[18] mounted a phase III trial comparing paclitaxel 225 mg/m^2 alone with combination paclitaxel at an identical dose with carboplatin (AUC, 6). Both regimens were administered at 3-week intervals. Final results revealed a significant improvement in response rate and MS for those enrolled in the combination arm, but OS was not significantly better. However, PS-2 individuals receiving combination paclitaxel/carboplatin had an MS nearly double that observed for those receiving paclitaxel alone (4.7 *v* 2.4 months), with nearly doubled respective 1-year OS rates (18% *v* 10%; log-rank $P = .0123$). There were no 2-year survivors among the PS-2 individuals receiving paclitaxel alone, whereas nearly 10% in the combination therapy group survived 2 years.

These results suggest that combination platinum-based therapy is preferable to the single-agent nonplatinum partner. However, a randomized phase II trial reported by Kosimidis et al[19] failed to demonstrate a convincing benefit for combination therapy. One hundred two PS-2 individuals were randomly assigned to either gemcitabine alone, 1,250 mg/m^2 every two weeks (G), or an identical dose in combination with carboplatin (CbG; AUC, 3) on days 1 and 15. MS for the gemcitabine arm was 4.8 months, compared with 6.7 months for the combination. In addition, there was a trend toward improved response rate for the combination (14% *v* 4%). However, there was no difference in 1-year OS (17.8% for G *v* 20% for CbG), or for symptom improvement rate (71% *v* 67%). Although this study failed to demonstrate a convincing improvement in survival for the combination, both arms demonstrated fairly high disease-specific symptom benefit.

In other studies in advanced NSCLC, single-agent therapy has not proved favorable. On Southwest Oncology Group (SWOG) 0027, a mixed cohort of elderly (≥ 70 years) and PS-2 patients received three cycles of vinorelbine 25 mg/m^2 days 1 and 8 every 3 weeks followed by three predetermined cycles of docetaxel 35 mg/m^2 administered for three consecutive weeks once every 4 weeks. Of 125 patients enrolled, 44 had PS 2.[20] Response rate in this group was only 10%, with an MS of 4 months and a 1-year OS of 14%. In a separate trial by Lilienbaum et al,[21] PS-2 patients (median age, 75 years) received docetaxel, either weekly at 30 mg/m^2 days 1, 8 and 15 every 4 weeks or 75 mg/m^2 every 3 weeks (standard). Response rates were 17% and 18%, respectively, but 1-year OS rates were 4% and 5%, respectively, with an aggregate MS of only 2.4 months.

These results strongly underscore the need for a formal phase III trial in the PS-2 cohort comparing a nonplatinum single agent with a combination single agent and platinum regimen. Clearly, the potential pool of patients eligible for such an effort is large; others have documented that at least 30% of those newly diagnosed with NSCLC are PS 2.[22]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Administrative support: Corey Langer
Collection and assembly of data: Corey Langer
Manuscript writing: Corey Langer, Sigui Li, Joan Schiller, William Tester, Bernardo L. Rapoport, David H. Johnson
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