Original Article

Nab-Paclitaxel in Older Patients With Non–Small Cell Lung Cancer Who Have Developed Disease Progression After Platinum-Based Doublet Chemotherapy

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BACKGROUND: The selection of later-line treatment for older patients with AJCC (version 7) stage IV non–small cell lung cancer (NSCLC) remains controversial. Nanoparticle albumin–bound (nab)-paclitaxel is approved with carboplatin for the first-line treatment of patients with NSCLC and subgroup analysis of phase 3 data has suggested superior survival in older patients. **METHODS:** The authors conducted a phase 2 study of nab-paclitaxel in 42 patients aged ≥70 years who had been treated previously with a platinum doublet regimen; patients also could have received a PD-1 inhibitor. The primary endpoint of the current study was grade 3 to 5 toxicity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0]). In addition to response rate, progression-free survival (PFS), and overall survival (OS), geriatric assessments also were performed before and during treatment, associations between baseline sarcopenia and outcomes were explored, and changes in T lymphocyte p16 before and during treatment were measured. The authors also performed a retrospective subgroup analysis of 19 older patients who were treated with nab-paclitaxel as part of a larger, randomized, phase 2 study; data were not combined. **RESULTS:** The rate of grade 3 to 5 toxicities was 33.7%. The most common grade 3 to 5 toxicities were decreased white blood cell count (11.9%), neutropenia (9.5%), and fatigue (11.9%). The response rate was 34.2% (2.6% complete response rate and 31.6% partial response rate). The median PFS was 5.2 months and the median OS was 9.3 months. Adverse prognostic factors were common: 42% of patients were frail and 39% of patients were prefrail, whereas 21% had an Eastern Cooperative Oncology Group performance status of 2 and 27% were sarcopenic. Only frailty was found to be predictive of inferior survival. A subgroup analysis of 19 older patients treated with nab-paclitaxel alone in a prior trial demonstrated a response rate of 15.8%, a PFS of 4.2 months, and an OS of 13.6 months. **CONCLUSIONS:** Fit and prefrail older patients with stage IV NSCLC should be considered for treatment with nab-paclitaxel after disease progression with doublet chemotherapy. ***Cancer*** **2020;126:1060-1067**.

KEYWORDS: elderly, geriatric assessment, lymphocyte p16, nanoparticle albumin–bound (nab)-paclitaxel, non–small cell lung cancer (NSCLC), sarcopenia.

INTRODUCTION

The median age at the time of presentation of stage IV non–small cell lung cancer (NSCLC) is 71 years,[1] making older adults not a niche subgroup but rather the dominant demographic. Nonetheless, because these patients historically have not been well represented in clinical trials, optimal treatment remains controversial. The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS)[2] trial demonstrated superior survival and quality of life with first-line vinorelbine compared with placebo. These findings were extended in the IFCT-0501 trial, which demonstrated that, similar to younger patients, fit older patients survived longer with treatment with first-line, platinum-based doublet therapy compared with single-agent therapy.[3] Despite the growing attention paid to initial systemic therapy options for older patients with advanced NSCLC, to our knowledge controversy remains regarding subsequent therapy.

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At the time of study design, the second-line options approved by the US Food and Drug Administration included pemetrexed, docetaxel, and erlotinib. Because pemetrexed is most commonly used in first-line therapy as part of a platinum doublet and because erlotinib is reported to have very limited activity in patients with *EGFR* wild-type tumors, docetaxel (with or without ramucirumab) has been left as the major treatment option for the majority of patients. Unfortunately, progression-free survival (PFS) and overall survival (OS) with docetaxel are short and toxicity often is prohibitive for the older patient. Therefore, there was an unmet need for more effective and less toxic options. We conducted a phase 2 study (LCCC 1210; ClinicalTrials.gov identifier NCT01702844) of nab-paclitaxel for patients with stage IV NSCLC and disease progression after platinum doublet chemotherapy.

During the conduct of the current trial, a randomized phase 2 study (ABOUND.2L+[4]) was completed that compared nanoparticle albumin–bound (nab)-paclitaxel alone with nab-paclitaxel with CC-486 (an oral formulation of 5-azacytidine) in patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 with advanced stage NSCLC after progression on platinum doublet chemotherapy.[4] A total of 19 patients were aged ≥70 years and were treated with nab-paclitaxel alone. In the current study, we have presented the treatment outcomes of these patients as an independent data source regarding outcomes with nab-paclitaxel as second-line therapy in older patients.

Nab-paclitaxel delivers paclitaxel bound to albumin, obviating the need for the toxic solvent cremophor. In a phase 3 study comparing carboplatin plus nab-paclitaxel with carboplatin plus cremophor-solvent paclitaxel, there was less neuropathy and neutropenia reported with the use of nab-paclitaxel, but more thrombocytopenia and anemia.[5] In the subgroup of patients aged ≥70 years, survival was improved from 10.4 months with carboplatin and paclitaxel to 19.9 months with carboplatin and nab-paclitaxel. We hypothesized that as a single-agent therapy in the second-line treatment of older patients, nab-paclitaxel would have a toxicity profile that was more favorable than that expected with docetaxel while at least maintaining survival.

Although fit older patients clearly benefit from treatment, increasing age is characterized by increased comorbidities and poorer tolerance to cytotoxic chemotherapy. Response and toxicity vary greatly among older individuals and tolerance to chemotherapy is poorly predicted by chronologic age and performance status.[6] We also sought to explore several other clinical and biologic markers as predictors of toxicity, including baseline geriatric assessment, sarcopenia, and T-lymphocyte p16INK4a expression, a biomarker of aging. Sarcopenia has been shown to be predictive of an increased toxicity to cytotoxic chemotherapy and inferior survival.[7-9] This likely reflects the combined effects of preexisting cancer cachexia as well as the effects of decreased muscle mass on chemotherapy metabolism. However, sarcopenia does not correlate well with physical function.[10] Therefore, we also evaluated geriatric assessments. Components of the geriatric assessment have been shown to be predictive of severe chemotherapy toxicity[6] and have been found to be feasible for trial implementation.[11] Lymphocyte p16INK4a has been shown to correlate with aging, doubling every decade with a further increase with physiologic stressors such as smoking.[12] Lymphocyte p16INK4a has been shown to increase with anthracycline therapy[13] and with bone marrow transplantation.[14] During the conduct of the current study, agents that inhibit PD-1 on T lymphocytes were approved, thereby further increasing our interest in understanding the impact of nab-paclitaxel on the biologic age of T lymphocytes.

MATERIALS AND METHODS

Study Design and Patients

The current study was approved by the University of North Carolina Lineberger Comprehensive Cancer Center Protocol Review Committee and the University of North Carolina institutional review board and the relevant regulatory bodies at each collaborating site. It was conducted in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT01702844).

Patients were required to have histologically or cytologically confirmed NSCLC and stage IV disease that had progressed during treatment with a nontaxane standard platinum doublet. Patients with *EGFR*, *EML4/ALK*, and *ROS1* were not excluded from the current study provided they also had experienced disease progression while receiving targeted therapy. An ECOG PS of 0 to 2 was allowed. Standard end-organ functions were required: an absolute neutrophil count >1500 cells/mm^3, hemoglobin >9 g/dL (it was acceptable to reach this through transfusion), platelet count >100,000 cells/mm^3, creatinine <1.5 mg/dL, total bilirubin <1.5 mg/dL, alkaline phosphatase <2.5 times the upper limit of normal (ULN), alanine aminotransferase <2.5 times the ULN, and aspartate aminotransferase <2.5 times the ULN. Patients with peripheral

neuropathy of grade ≥2 were excluded. Additional details regarding trial conduct are available in the full protocol in Supporting appendix 1.

During the conduct of the current study, PD-1 inhibitors were approved and the study was amended to allow for the enrollment of patients who had developed disease progression while receiving immunotherapy in addition to a cytotoxic doublet regimen.

Treatment and Assessments

Nab-paclitaxel was administered at a dose of 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Imaging was performed every other cycle. Treatment was continued until intolerance, disease progression, or patient withdrawal. Dose modifications were allowed, with details regarding the full protocol shown in Supporting Table 1. Geriatric assessment was acquired at baseline and, when possible, at the end of treatment. Lung Cancer Symptom Scales and Functional Assessment of Cancer Therapy–Lung (FACT-L) and lymphocyte p16 were acquired at baseline and before odd numbered cycles. Sarcopenia analysis was performed at baseline and at the time of first imaging (prior to cycle 3).

Outcomes and Statistical Analyses

The primary endpoint of the current study was the occurrence of treatment-related toxicities of grade ≥3 after 6 cycles, or 3 weeks after the discontinuation of treatment for those who came off treatment earlier. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The null hypothesis was that the rate of grade 3 to 5 toxicity would be 60% (Scott Barker [Eli Lilly], e-mail communication, November 19, 2011) and this was tested against the 1-sided alternative that it was lower. A Simon 2-stage design with a relaxed futility stopping rule[15] was used. In the first stage, toxicity was assessed after the second cycle, or 3 weeks after the discontinuation of treatment for those who came off treatment earlier. In the second stage, toxicity was determined after 6 cycles, or 3 weeks after the discontinuation of treatment for those who came off treatment earlier. In the first stage, a total of 25 patients were accrued. Because there were >10 patients who were free of grade 3 to 5 toxicity, an additional 17 patients were accrued for a total of 42 patients. The null hypothesis was prespecified to be rejected if ≥23 patients were free of grade 3 to 5 toxicities after 6 cycles, or 3 weeks after the discontinuation of treatment for those patients who came off treatment earlier. Assuming that the toxicity-free rate after 2 cycles has a uniform distribution (0, 0.3) under the null hypothesis, and can be at most 40% under the alternative, this design yielded a type I error rate of at most 0.0375 and a power of at least 80% when the true toxicity-free rate was 60%.

Secondary clinical endpoints included OS and PFS, which were estimated using the Kaplan-Meier method. Cox proportional hazards modeling was used for comparisons by patient covariates. The response rate was measured using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), with the exact binomial confidence interval provided. Wilcoxon rank sum tests were used to compare FACT-L and Lung Cancer Symptom Scale score changes.

The expression of p16INK4a in T lymphocytes was measured as previously reported.[13] Briefly, CD3-positive T cells were isolated from whole blood using the RosetteSep Human T Cell Enrichment Cocktail (StemCell Technologies Inc, Cambridge, Massachusetts) within 8 hours of blood draw. Cells were isolated and stored frozen at −80 °C. Gene expression in T-cell RNA was measured using TaqMan quantitative reverse-transcriptase–polymerase chain reaction. T-cell purity in clinical trial samples was monitored using measuring expression of the gamma subunit of the CD3. p16 expression was calculated through normalizing to housekeeping genes and was reported as log2 and an absolute value.

Sarcopenia was measured at the first lumbar (L1) level as previously reported.[16] Baseline computed tomography scans were reviewed and images at L1 were extracted manually into Digital Imaging and Communications in Medicine (DICOM) format. These tomograms then were read into the Slice-O-Matic software (TomoVision, Magog, Quebec, Canada) and automatically analyzed using the ABACS L3 plug-in (Voronoi Health Analytics, Coquitlam, BC, Canada) to tag muscle. Each image was reviewed manually and adjusted as necessary to accurately capture only muscle. Smooth muscle mass was expressed in squared centimeters.

The geriatric assessment tool has been described previously.[11,17] Briefly, the tool assessed functional status, comorbidity, psychological state, social support, nutritional support, medications, Timed Up and Go test, and the Blessed Orientation-Memory-Concentration test.

Subgroup Analysis of ABOUND.2L+

We also conducted a subgroup analysis of patients aged ≥70 years who were treated with nab-paclitaxel alone on the randomized phase 2 ABOUND.2L+ study. Details of the conduct of the study and its primary results have been published previously.[4] It is interesting to note that, in the ABOUND.2L+ study, nab-paclitaxel was administered at

a dose of 100 mg/m^2 on days 1 and 8 of a 21-day cycle, in contrast to the LCCC 1210 schedule described above. In the current study, we reported the response rate, PFS, and OS results for patients aged ≥70 years who were treated using second-line therapy with nab-paclitaxel alone on the ABOUND.2L+ study. Given the limited patient numbers, no combined analysis was attempted.

RESULTS

A total of 42 patients were accrued between June 2013 and April 2017 at the Cleveland Clinic (Cleveland, Ohio), the University of North Carolina Lineberger Comprehensive Cancer Center (Chapel Hill, North Carolina), the University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania), Highlands Oncology (Fayetteville, Arkansas), Bon Secours (Midlothian, Virginia), Rex Hematology Oncology Associates (Raleigh, North Carolina), and the Swedish Cancer Institute (Seattle, Washington). Patient demographics are shown in Table 1. The mean age of the patients was 76 years (range, 71-84 years). Patients with an ECOG PS of 2 represented approximately 21% of the sample. Geriatric assessment at baseline showed 19% of the population to be robust, 39% to be prefrail,[18] and 42% to be frail. Approximately 27% of patients were sarcopenic. The mean baseline lymphocyte p16 expression, expressed as the log2 of reverse transcriptase–polymerase chain reaction, was 11.06 (Fig. 1). Lymphocyte p16 values did not, on average, decrease during treatment (median change, 0.11; interquartile range, −0.24 to 0.26).

The primary objective of the current study was to evaluate the rate of grade 3 to 5 toxicity. Approximately 66.7% of patients (28 of 42 patients) were free of grade 3 to 5 toxicity and therefore the current study met its primary endpoint. Adverse events that occurred at any grade in at least 10% of patients or in at least 1 patient at grade 3 to 5 are shown in Table 2. The most common adverse events were hematologic. One patient died of infection leading to sepsis.

The objective response rate was 34.2% (13 of 38 patients [1 complete response and 12 partial responses]; 95% CI, 19.6%-51.4%). In addition, 15 patients (39.5%) achieved stable disease, for a disease control rate of 73.7%; this is shown in greater detail in Figure 2. The median PFS was 5.2 months (95% CI, 2.0-7.4 months) and the median OS was 9.3 months (95% CI, 6.4-2.1 months) (Fig. 3). Similar results were found in the 19 patients in the retrospective subgroup analysis from the Abound.2L+ study. Among these patients, the objective response rate was 15.8% (3 of 19 patients, all of whom achieved partial responses; 95% CI, 3.5%-39.6%), the median PFS was 4.2 months (95% CI, 2.6-5.1 months), and the median OS was 13.6 months (95% CI, 5.3 months to not reached) (see Supporting Figs. 1 and 2, respectively).

TABLE 1. Demographic Characteristics (N = 42)

Variable	No.	Percentage
Age, y	Mean, 76.3	Range, 71-84
Race		
Black or African American	7	17%
White	35	83%
Sex		
Female	22	52%
Male	20	48%
Smoking status		
Never	4	10%
Former/current	38	90%
ECOG PS		
Fully active (0)	5	12%
Restricted (1)	28	67%
2	9	21%
Exercise at least 10 min/d		
Never	10	46%
Few times per mo	3	14%
1-2 times per wk	6	27%
3-4 times per wk	2	9%
≥5 times per wk	1	5%
Drink alcohol		
No	13	57%
Yes	7	13%
Almost never	7	30%
Histology		
Adenocarcinoma	35	83%
Squamous cell carcinoma	7	17%
Prior cytotoxic regimens		
Carboplatin plus pemetrexed	26	62%
Carboplatin, pemetrexed, and bevacizumab	4	9.5%
Cisplatin plus pemetrexed	1	2%
Carboplatin plus gemcitabine	11	26%
Prior nivolumab	8	19%
Prior erlotinib	1	2%
Other prior regimens	3	7%
Best response to prior therapies		
CR	0	0%
PR	3	5.5%
SD	16	30%
PD	22	41%
Unknown/not evaluable	13	24%
Frailty index (n = 26)		
Robust (0 to <0.2)	5	19%
Prefrail (0.2-0.35)	10	39%
Frail (>0.35)	11	42%

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease.

A total of 17 patients subsequently received systemic therapy. Six patients received gemcitabine, 5 patients received nivolumab, 2 patients received carboplatin plus pemetrexed, 2 patients received erlotinib, 1 patient received osimertinib, and 1 patient received nab-paclitaxel. Five patients were treated after the study with radiotherapy. No patient was treated surgically.

As exploratory objectives, age, ECOG PS, frailty index, baseline weight, baseline body surface area, baseline sarcopenia, and baseline lymphocyte p16 were evaluated

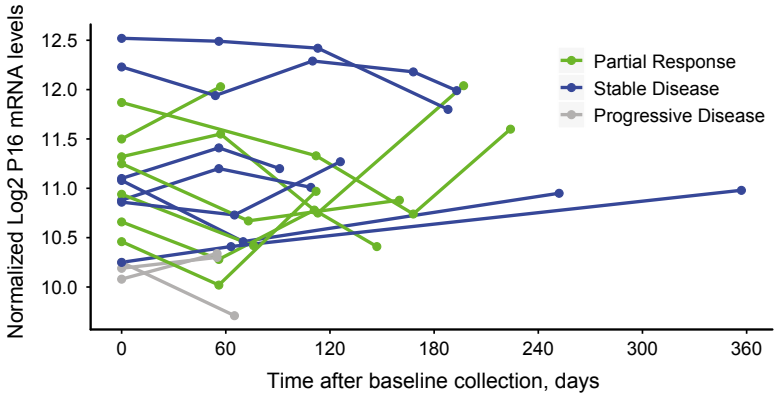

Figure 1. Lymphocyte p16 values over time. mRNA indicates messenger RNA.

TABLE 2. Adverse Events Occurring in at Least 10% of Patients at Any Grade or in at Least 1 Patient at Grade ≥3[a]

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematologic					
Anemia	5 (12%)	8 (19%)	2 (5%)	0	0
Decreased WBC	5 (12%)	5 (12%)	4 (10%)	1 (2%)	0
Neutropenia	4 (10%)	6 (14%)	3 (7%)	1 (2%)	1 (2%)
Lymphopenia	3 (7%)	2 (5%)	2 (5%)	0	0
Metabolic					
Low albumin	4 (10%)	0	0	0	0
Low magnesium	3 (7%)	1 (2%)	0	0	0
Hypercalcemia	0	0	1 (2%)	0	0
Hypophosphatemia	0	0	1 (2%)	0	0
Other toxicity					
Fatigue	8 (19%)	9 (21%)	5 (12%)	0	0
Peripheral sensory neuropathy or paresthesia	8 (19%)	7 (17%)	2 (5%)	0	0
Alopecia	6 (14%)	5 (12%)	0	0	0
Nausea	7 (17%)	3 (7%)	0	0	0
Constipation	6 (14%)	0	0	0	0
Limb edema	6 (14%)	0	0	0	0
Peripheral motor neuropathy	2 (5%)	1 (2%)	1 (2%)	0	0
Generalized muscle weakness	0	1 (2%)	2 (5%)	0	0
Myocardial infarction	0	0	0	1 (2%)	0

Abbreviation: WBC, white blood cell.
[a]Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

as potential predictors of grade 3 to 5 toxicity, response, PFS, and OS (Fig. 1). Lymphocyte p16 at baseline was higher than found previously in healthy patients without cancer (median, 10.88; range, 10.08-12.52), and did not appear to increase significantly with treatment (median increase of 0.26; range, −0.72 to 0.73). Baseline lymphocyte p16 was lowest in those patients who had progressive disease ($P = .02$). Patients who were frail had inferior survival (median OS, 7.5 months vs 14.2 months; $P = .045$). Otherwise, none of the objectives was found to meaningfully or significantly associated.

Quality of life was assessed using the FACT-L and symptoms were assessed using the Lung Cancer Symptom Scale. Neither quality of life measures nor symptom measures were found to change meaningfully or significantly from baseline to the time of first disease assessment. Because patients were on the study for variable times and due to the small size of the current study, subsequent data were not meaningful.

DISCUSSION

Prior to the conduct of the current trial, docetaxel was the most commonly used second-line treatment. Although PD-1 inhibitors were for a time the dominant standard of care in second-line treatment, their approval together with platinum doublet chemotherapy will likely restore docetaxel (alone or with ramucirumab) to its role as the dominant next-line therapy. In what to our knowledge is

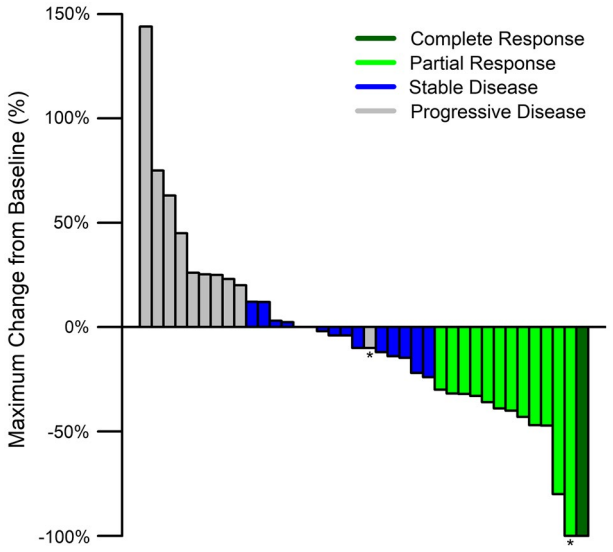

Figure 2. Waterfall plot. It is interesting to note that 1 patient demonstrated a 100% reduction in target lesions, but was considered to have a partial response due to the persistence of non–Response Evaluation Criteria in Solid Tumors (RECIST)-measurable disease. Another patient with a reduction in disease burden was considered to have progressive disease due to progression in nonmeasurable lesions. These subjects are indicated with an asterisk.

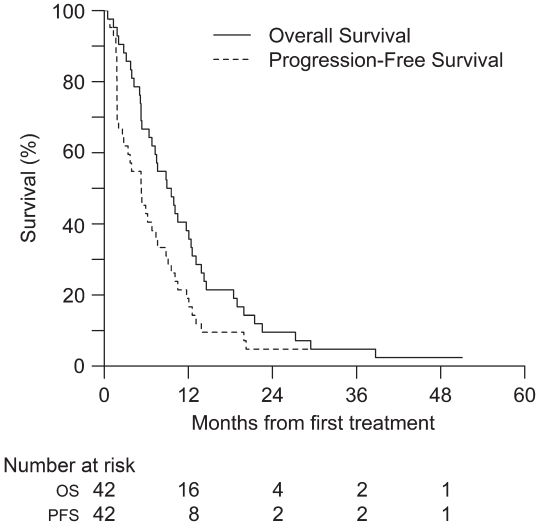

Figure 3. Progression-free survival (PFS) and overall survival (OS).

the most recent large trial of docetaxel performed prior to the current study,[19] the rate of grade 3 to 5 toxicity was approximately 60% in patients aged ≥65 years and this formed the null hypothesis for the prospective phase 2 LCCC 1210 trial. Similar results have since been reported with docetaxel[20-22] and, as might be expected, were even higher with the addition of ramucirumab.[23] Nab-paclitaxel resulted in a grade 3 to 5 toxicity rate of approximately 33%, thereby meeting the primary statistical endpoint of the current trial. In addition to the more severe toxicities, the lower grade toxicity profile also is acceptable and consistent with the profile of nab-paclitaxel known from multiple trials[19-22] and clinical use. In particular, grade 3 to 5 neutropenia occurred in approximately 10% of patients in the current study compared with 30% in historic controls with docetaxel.[19] Conversely, neuropathy was common, with approximately 60% of patients experiencing any grade of neuropathy, but only 5% reporting grade 3. Thrombocytopenia was rare, with a rate of 7% of grade 1 and no higher-grade reactions.

The primary endpoint of the current study, the avoidance of grade 3 to 5 toxicities, was chosen based on a cultural belief among many in the oncologic and lay communities that the avoidance of toxicity should be the primary consideration in the selection of therapy for the older patient. In addition, the prevention of disease-related suffering and the extension of the duration of life are important and can be driven by disease control. PFS with docetaxel in the second-line setting has ranged from 2.8 months to 4.2 months and OS has ranged from 6 months to 9.4 months in patients unselected by age.[19-22] In the prospective LCCC 1210 trial, the median PFS was 5.2 months and the median OS was 9.3 months. These results are supported further by subgroup analysis from the Abound.2L+ study, in which the PFS was 4.2 months and the OS was 13.6 months. This work was initiated based on subgroup analysis from a phase 3 study of carboplatin plus paclitaxel versus carboplatin plus nab-paclitaxel demonstrating superior OS in older patients.[5] The data from both the LCCC 1210 and ABOUND.70+ studies support this hypothesis, but only a randomized study of another taxane compared with nab-paclitaxel could truly confirm it. We did note that another study (the phase 4 ABOUND.70+ study[24]) also was consistent, with a survival of 15.2 months to 16.2 months reported in older patients who were treated with carboplatin and nab-paclitaxel as first-line therapy.

The current study is unique in that patients with an ECOG PS of 2 were eligible. In addition, geriatric assessment confirmed that many of the trial patients were prefrail and frail. Analysis of novel measures of geriatric fitness such as sarcopenia and lymphocyte p16 further support that the sample of patients in the current study was representative.

Muscle mass is lost beginning in middle age into old age. Sarcopenia previously has been shown to be predictive of poor outcomes in patients undergoing treatment of NSCLC. In the current study, we hypothesized that toxicity would be worse in sarcopenic patients. However, the smooth muscle index was identical between those with and without grade 3 to 5 toxicities. Sarcopenia also failed to predict any disease-related outcomes.

The current study was powered to evaluate toxicity, and thus analyses related to geriatric assessment, sarcopenia, lymphocyte p16, and quality of life can only be considered as exploratory. Lack of associations cannot be taken to indicate that none exist, simply that the current study sample was too small to make reliable conclusions. We encourage the integration of geriatric assessment and novel biomarkers into larger studies of geriatric patients with lung cancer. We further note that the total number of patients with an ECOG PS of 2 was small, thereby resulting in an inability to make reliable conclusions regarding efficacy or safety in this subgroup.

Lymphocyte p16 is an intriguing biomarker of aging in that it increases exponentially with chronologic age and is influenced by factors known to increase physiologic age, such as smoking and exposure to cytotoxics (eg, anthracyclines). In contrast to anthracycline-based therapy, nab-paclitaxel did not appear to age peripheral blood T cells during treatment. This could be due to a plateau effect in which subsequent therapy does not age the immune system or, alternatively, nab-paclitaxel may not age older patients with lung cancer biologically.

The results of the current study support a broad body of data[2,3,24,25] demonstrating that chronologic age alone should not be used as a selection factor and that older patients can benefit from additional therapy after treatment with a platinum doublet. Although not definitive due to the nonrandomized nature of the data, the PFS and OS data from these 2 separate data sources further support the existing literature suggesting the promising efficacy of nab-paclitaxel in older patients with lung cancer. Studies of real-world databases are planned to further address this question.

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CONFLICT OF INTEREST DISCLOSURES

Jared M. Weiss has received grants from Celgene for work performed as part of the current study and has received personal fees from AstraZeneca, Regeneron, and EMD Serono; grants and honoraria from Celgene and Pfizer; and grants from Merck and Novartis for work performed outside of the current study. Nathan Pennell received a grant to his institution from Celgene to cover the trial expenses for the current study, for which he was the local principal investigator, and has acted as a member of the advisory boards for AstraZeneca, Merck, and Regeneron and as a paid consultant for Eli Lilly for work performed outside of the current study. Daniel Morgensztern has acted as a paid member of the advisory boards for AbbVie, Bristol-Myers Squibb, Takeda, and PharmaMar for work performed as part of the current study. Howard Jack West has received honoraria for acting as a paid consultant and member of the Speakers' Bureau for Ariad/Takeda, AstraZeneca, Genentech/Roche, and Merck and has acted as a paid consultant for Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, LOXO, Pfizer, and Spectrum for work performed outside of the current study. James P. Stevenson has acted as a paid member of the advisory board for AstraZeneca and has received grants to his institution from Merck and Company, Bristol-Myers Squibb, and Bayer Healthcare for work performed outside of the current study. Tom Stinchcombe has acted as a paid member of the advisory boards for Takeda, AstraZeneca, Novartis, Genentech/Roche, and G1 Therapeutics and has received research funding to his institution from Genentech/Roche, Blueprint Medicines, Merck, AstraZeneca, and Takeda for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jared M. Weiss, **Allison M. Deal**, and **Hyman B. Muss** designed the current study. All authors contributed to data generation, data analysis, and article writing and editing.

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