

Sequential Vinorelbine and Docetaxel in Advanced Non-small Cell Lung Cancer Patients Age 70 and Older and/or with a Performance Status of 2: A Phase II Trial of the Southwest Oncology Group (S0027)

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Background: This phase II study (S0027) evaluated the efficacy and tolerability of planned sequential single-agent chemotherapy with vinorelbine followed by docetaxel in patients with advanced non-small cell lung cancer (NSCLC) age 70 and older and/or a performance status (PS) of 2.

Methods: Patients with stage IIIB (pleural effusion) or stage IV NSCLC, age 70 and older with a PS of 0-1 or 2, any age, received three cycles of vinorelbine 25 mg/m² days 1 and 8 every 21 days followed by three cycles of docetaxel 35 mg/m² days 1, 8, and 15 every 28 days.

Results: A total of 125 patients entered the study; 117 patients were assessable for response, survival, and toxicity. Seventy-five patients were in stratum 1 (age 70 and older, PS 0-1) and 42 patients in stratum 2 (PS 2, any age). Objective response was 19% (95% confidence interval [CI]: 11%–30%) and 11% (95% CI: 3%–25%) in strata 1 and 2, respectively. Median survival was 9.1 months (95% CI: 7.1–12.7) and 5.5 months (95% CI: 3.1–6.5) in strata 1 and 2, respectively. Survival at 12 months was 41% and 13% in strata 1 and 2, respectively. Grade 3/4 neutropenia was seen in 32% and 31% of patients in strata 1 and 2, respectively. Three deaths probably related to treatment were noted: one in stratum 1 and two in stratum 2.

Conclusion: Sequential vinorelbine and docetaxel is a well-tolerated and effective regimen in comparison with reports of other treatments tested in patients with advanced NSCLC age 70 and older and/or with a PS of 2.

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Treatment options for patients with advanced non-small cell lung cancer (NSCLC) remain inadequate at the present time. Meta-analyses have demonstrated a modest survival benefit for cisplatin-based combination chemotherapy regimens when compared with supportive care alone.^{1–4} The majority of patients in these clinical trials were younger than the age of 65, had a good performance status (PS), and had few major comorbid conditions. The value of chemotherapy in other populations with advanced NSCLC such as the elderly, patients with a poor PS, and those with defined comorbid conditions has until recently received scant attention.

Individuals older than age 65 comprise a disproportionately large share of the patient population with newly diagnosed cancer, including NSCLC. Despite the preponderance of older individuals with cancer, cooperative group trials in the United States enroll relatively modest proportions of elderly patients (defined here as age 70 and older). An analysis conducted by the Southwest Oncology Group (SWOG) demonstrated that only 13% of all patients enrolled into SWOG trials were age 70 and older, although the overall proportion of United States cancer patients age 70 and older during that time period was 47%.⁵ When analyses are confined to lung cancer, the proportion of patients age 70 and older entered into recent cooperative group trials in advanced NSCLC in the United States has, with rare exception, been ≤20%.^{6–9}

Recently, a number of prospective trials targeting older patients with advanced NSCLC have been reported.^{10–14} These trials have demonstrated the value of modern single-agent chemotherapy and on balance would suggest no advantage for nonplatinum combinations versus single-agent therapy. Vinorelbine, gemcitabine, and the taxanes all appear to be useful and well-tolerated agents. Retrospective subset analyses from recent cooperative group trials suggest reason-

able tolerance and potential benefit for platinum-based combinations in older patients as well.⁶⁻⁹ To date, however, no prospective trial comparing a single agent with a platinum-based combination has been reported in older patients with advanced NSCLC.

Patients with a PS of 2 comprise another substantial subset of the advanced stage NSCLC population that until recently has been largely excluded from clinical trials. The prognostic importance of an impaired performance status in NSCLC is well established. A trial performed by the Eastern Cooperative Oncology Group (ECOG) in the early 1980s evaluating four different chemotherapy regimens demonstrated median survival times of 36, 26, and 10 weeks for PS 0, 1, and 2 patients, respectively.¹⁵ Subset analyses from a number of other trials also suggested that chemotherapy results in excessive toxicity and limited treatment benefit in the PS 2 population. Recently, interest in the role of chemotherapy for PS 2 patients with NSCLC has also increased due to the availability of a number of well-tolerated newer agents such as vinorelbine and docetaxel.^{14,16-18} In addition, a retrospective analysis from a recently reported phase III trial comparing the combination of paclitaxel plus carboplatin with paclitaxel alone revealed a similar degree of benefit for the combination versus the single agent in both good PS patients and in PS 2 patients.⁹ Nevertheless, virtually no prospective trials targeting PS 2 patients have been conducted to date. Therefore, there is a paucity of data to guide clinicians on both the potential value and tolerability of chemotherapy in this patient population.

One approach to potentially maximize therapeutic benefit while maintaining excellent tolerance involves the use of drugs with demonstrated value as single agents in a planned sequential fashion rather than concurrently. Models described by Day and by Norton and Simon, as well as preliminary clinical data, support the concept that sequential administration of chemotherapeutic agents may be a superior approach to concurrent administration.¹⁹⁻²³ Both models postulate that the planned substitution of new drugs before the emergence of clinical resistance may be a viable alternative to concurrent administration of the same agents. Recent trials in breast-cancer and NSCLC suggest benefit for the sequential administration of chemotherapy agents.^{24,25}

With this background, we initiated a trial of planned sequential single-agent chemotherapy in patients with advanced NSCLC age 70 and older and/or with a PS of 2. Given the experience with vinorelbine and docetaxel as first-line therapy in these patient populations, the proven activity of docetaxel as second-line therapy in NSCLC, and our use of docetaxel sequentially in S9504 and S9806, these agents were deemed appropriate for sequential use in this trial. Therefore, it was elected to employ a schedule of three cycles of vinorelbine followed by three cycles of docetaxel in the current study. In addition to the usual endpoints of survival and disease response, a patient report of the impact of treatment was also incorporated into the study design.

PATIENTS AND METHODS

Eligibility

Patients were required to have histologically or cytologically documented newly diagnosed selected stage IIIB (malignant pleural effusion or multiple lesions in a single lobe) or stage IV advanced NSCLC or recurrent disease after previous surgery and/ irradiation. Patients had to meet one of the two following criteria: (1) age 70 and older and a Zubrod PS of 0-1 or (2) a Zubrod PS of 2, any age. All patients were required to have measurable or nonmeasurable but assessable disease, be 18 years of age and older, and have acceptable hepatic and hematologic function. Patients with brain metastases, grade 2 and higher symptomatic neuropathy, previous chemotherapy or biological therapy for NSCLC, or active pregnancy were ineligible for inclusion in the trial. The study was approved by the institutional review boards of the respective institutions, and all patients gave written informed consent.

Treatment Plan

Patients received vinorelbine 25 mg/m² intravenously on days 1 and 8 of a 21-day cycle for three cycles, followed by docetaxel 35 mg/m² on days 1, 8, and 15 of a 28-day cycle for three cycles. Patients with early evidence of disease progression before receiving all three cycles of vinorelbine were to be immediately sequenced to docetaxel. Treatment was limited to six total cycles of therapy. Treatment at the time of disease recurrence or progression after six cycles was at the discretion of each treating physician.

Dose Modifications

Patients experiencing a nadir granulocyte count of <500/ μ L or a nadir platelet count of <50,000/ μ L or requiring a 2-week or longer delay in hematologic recovery were required to undergo a 25% dose reduction. Treatment was omitted on day 8 and/or day 15 if the absolute granulocyte count was <1500/ μ L and/or the platelet count was <100,000/ μ L. Patients who experienced grade 2 or higher neurologic toxicity had treatment held until symptoms reached grade 0-1. If time to recovery was 4 weeks or longer, the patient was removed from the study. Patients who again experienced grade 2 or higher neurologic toxicity with re-treatment were removed from protocol. Dose modifications for hepatic dysfunction related to docetaxel were specified in the protocol. For other toxicities, doses were either held for patients with grade 2-3 toxicities or decreased by 25% (depending on the nature of the toxicity). For patients with grade 4 toxicity, doses were held until resolution of the toxicity to grade 1 or lower.

Response and Toxicity Criteria

Patients were evaluated for disease response after three cycles of vinorelbine and again after three cycles of docetaxel. Response was assessed using RECIST (Response Evaluation Criteria in Solid Tumors) criteria,²⁶ and toxicities were assessed using National Cancer Institute Common Toxicity Criteria Version 2.0.²⁷

Ancillary Treatment

During docetaxel treatment, patients also received dexamethasone 4 mg orally for three doses (the evening before treatment, the morning of treatment, and the evening of the day of treatment). Patients developing fluid retention related to docetaxel could receive diuretics at the discretion of the investigator. The routine use of granulocyte colony-stimulating factor was not permitted. Erythropoietic growth factors were permitted.

Patient Report Measures

Functional and symptom status

The Functional Assessment of Cancer Therapy–Lung (FACT-L) is a validated tool used in lung cancer clinical trials and has documented psychometric properties including sensitivity to change.^{28–32} Given that patients in this study could have a PS of 2 and/or be 70 years of age and older, we used an abbreviated version of the FACT-L that would reduce patient burden. The Trial Outcome Index (TOI) includes three subscales from the FACT-L; seven functional, seven physical well-being, and seven lung cancer-specific items.^{29,30} The primary patient-reported outcome measure was the FACT-L TOI total score; higher scores reflect better functional and symptom status. The FACT-L TOI was completed by patients prestudy and at the beginning of cycles 2 through 6 and at completion of protocol treatment after the third dose of docetaxel for a total of seven assessments.

Comorbidity

The Medical Conditions Questionnaire developed by Katz et al.³³ was administered once at study entry for use as a covariate in analyses. The scoring algorithm based on the Katz et al. scoring system incorporates severity of medical conditions; higher scores reflect more severe comorbid conditions. We also calculated a count of organ systems affected by a medical condition.

Statistical Considerations

The main objective of the study was to test whether the sequential combination of vinorelbine and docetaxel has promise in terms of increasing survival in the advanced NSCLC subsets of elderly patients with PS 0-1 and PS 2 patients of any age and to distinguish any differences between these two subsets in terms of efficacy and toxicity. Because it is assumed that PS 2 patients have a poorer prognosis, patients were accrued into two strata: stratum 1, age 70 and older, PS 0-1; stratum 2, PS 2, any age.

In stratum 1, the regimen would be considered promising if the true median survival from registration was ≥ 6 months in conjunction with acceptable toxicity and would be considered of no further interest if the true median survival was ≤ 4 months. With ≥ 55 patients accrued over 18 months, an additional 1-year follow-up and assuming exponential survival, the power of a one-sided 0.05 level test of 4- versus 6-month survival is at least 0.90. In stratum 2, the regimen would be considered promising if the true median survival from registration was ≥ 4 months in conjunction with acceptable toxicity and would be considered of no further interest if

the true median survival was ≤ 2.5 months in conjunction with acceptable toxicity. With ≥ 40 patients accrued over 12 months, an additional 1-year follow-up and assuming exponential survival, the power of a one-sided 0.05 level test of 2.5- versus 4-month survival is 0.90 or higher. Exploratory analyses were planned on the association of patient characteristics, such as age, PS, and comorbidity with survival, response rate, functional and symptom status, dose delivered, and toxicities.

Patient-reported outcomes: Fact-L TOI

FACT-L TOI submission rates were calculated for the two strata to indicate the proportion of forms submitted given that the patient was alive at a particular assessment time point. Linear mixed models for longitudinal data were employed for a first examination of the patient report of functional status data.³⁴ The patient reported outcomes analysis is preliminary, with ongoing determination of the robustness to different nonignorable missing data mechanisms.

Patient-reported outcomes: comorbidity

We examined the ability of patient-reported comorbid medical conditions to predict survival for patients within each stratum. Katz scores and counts of affected organ systems were used to indicate level of comorbidity; results were similar with both organ counts and the Katz et al. comorbid medical conditions score incorporating severity. The organ systems count and Katz scores were dichotomized as 0 or ≥ 1 organ systems and 0 or ≥ 1 , respectively, for survival comparisons.

RESULTS

Patient Characteristics

Between September of 2001 and June of 2003, 125 patients were registered in the study. Seven patients were ineligible for the following reasons: baseline disease assessments outside of time frame,³ brain metastases at baseline,¹ staging criteria not met,² NSCLC histology not demonstrated.¹ One additional patient did not receive any treatment (refused after consenting) and is not assessable. Characteristics of 117 eligible patients assessable for response/survival and toxicity are displayed in Table 1. Seventy-five patients were entered into stratum 1 (age 70 and older, PS 0-1) and 42 patients were entered into stratum 2 (PS 2, any age). Most patients (85%) had stage IV disease. The most common histologic subtype was adenocarcinoma, present in 50% of patients. Median age in strata 1 and 2 were 75 and 73 years, respectively. Twenty-three patients (20%) were age 80 years and older. Similar proportions of men (54%) and women (46%) participated in the trial.

Treatment Received

Treatment was completed as planned (six cycles) in 36 (48%) and 16 (38%) of patients in strata 1 and 2, respectively. The median number of cycles received was five in both strata. Thirty-one (41%) and 12 (29%) patients required dose reductions in strata 1 and 2, respectively.

TABLE 1. Patient Characteristics

Variable	Stratum	
	1 ^a	2 ^b
Total no. of patients	75	42
Gender, % male/female	53/47	55/45
Median age, y (range)	76 (70–88)	73 (44–85)
Stage, % IIIB/IV	14/86	15/85
Pathology, patients (%)		
Adenocarcinoma	37 (49)	21 (50)
Squamous	15 (20)	14 (33)
Large cell/other	22 (31)	7 (16)

^a Age 70 years and older, performance status 0-1. ^b Any age, performance status 2.

Comorbidity

Patients 70 years of age and older with a PS of 0-1 and a Katz score of 0 ($n = 34$) had a median survival of 11 months, whereas those with a score ≥ 1 ($n = 41$) had a median survival of 8 months ($p = 0.31$). When analyzed by number of organ systems affected by comorbid conditions in this stratum, those with no comorbidities ($n = 20$) had a median survival of 13 months, and those with one or more affected organ systems ($n=55$) had a median survival of 8 months ($p = 0.19$). In PS 2 patients, those with a Katz score of ≥ 1 ($n = 11$) had a median survival of 6 months, whereas those with a Katz score of 0 ($n = 31$) had a median survival of 3 months ($p = 0.07$).

Toxicity

Treatment related toxicity (grade 3 or higher) is displayed in Table 2. Grade 3/4 neutropenia was seen in 32% and 31% of patients in strata 1 and 2 respectively. Other grade 3/4 adverse events were uncommon with the exception of fatigue and dyspnea. Three deaths probably related to treatment were noted. One patient in stratum 1 died of pneumonia. In stratum 2, there were two treatment related deaths: one patient with respiratory failure; one patient with renal failure, dyspnea and a cardiac conduction abnormality. Fourteen patients (19%) in the over-70 stratum and three

TABLE 2. Toxicity

	Stratum 1 ^a ($n = 75$)		Stratum 2 ^b ($n = 42$)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	2 (3%)	1 (1%)	3 (7%)	0
Fatigue/malaise	14 (19%)	2 (3%)	6 (14%)	1 (2%)
Febrile neutropenia	4 (5%)	0	1 (2%)	0
Nausea	4 (5%)	0	2 (5%)	0
Neutropenia	15 (20%)	9 (12%)	6 (14%)	7 (17%)
Sensory neuropathy	0	0	1 (2%)	0
Thrombocytopenia	0	0	0	0
Maximal grade, any toxicity	38 (51%)	19 (25%)	20 (48%)	11 (26%)

^a Age 70 years and older, performance status 0-1. ^b Any age, performance status 2.

patients (7%) in the PS-2 stratum went off study because of adverse events.

Response And Survival

Objective response to treatment for patients with measurable disease is displayed in Table 3. Fourteen patients (19%) (95% CI: 11%–30%) in the 70 years of age and older stratum and four patients (11%) (95% CI: 3%–25%) in the PS 2 stratum achieved partial responses. Fourteen patients in the 70 years of age and older stratum and five patients in the PS 2 stratum had inadequate assessments of response and are presumed nonresponders. Reasons for inadequate assessment were early discontinuation of treatment before the first disease assessment (nine cases), inability to assess due to a collapsed lung (one case), inadequate imaging of the primary tumor (one case), failure to properly follow all target and nontarget lesions (eight cases). Six patients were without measurable disease at trial entry and are not included in the calculation of a response rate. Median follow-up for surviving patients in strata 1 and 2 is 13.0 months (minimum, 6.3; maximum, 23.1) and 10.4 months (minimum, 7.0; maximum, 13.5), respectively. Median progression-free survival was 4.7 months (95% CI: 2.7-5.2 months) and 2.6 months (1.9-4.2 months) in strata 1 and 2, respectively. Figure 1 graphically displays overall survival. Median survival was 9.1 months (95% CI: 7.1–12.7) and 5.5 months (95% CI: 3.1–6.5 months) in strata 1 and 2, respectively. Survival at 12 months was 41% and 13% in strata 1 and 2, respectively. Survival at 24 months was 13% and 5% in strata 1 and 2, respectively.

Functional and Symptom Status

Submission rates (defined as the proportion of submitters among patients alive at each time point) for the seven FACT-L TOI assessments were as follows: stratum 1 (pre-study [100%]; weeks 4 [85%], 7 [82%], 10 [76%], 14 [69%], 18 [72%], and week 22 [51%]); stratum 2 (prestudy [100%]; weeks 4 [81%], 7 [82%], 10 [78%], 14 [88%], 18 [76%], and 22 [60%]). The percentage of patients submitting all required forms was not statistically different for the two strata (26% versus 24%).

Figure 2 shows the regression line from a linear mixed model of FACT-L score by assessment time, plotted over the mean FACT-L TOI scores at each time point, separately for each stratum. Patients in stratum 2 were more compromised at study entry than those in stratum 1: the stratum 2 mean

TABLE 3. Response

	Stratum 1 ^a ($n = 74$)	Stratum 2 ^b ($n = 37$)
Complete response	0	0
Partial response	14 (19%; 95% CI: 11%–30%)	4 (11%; 95% CI: 3%–25%)
Stable disease	22 (30%)	10 (27%)
Increasing disease	23 (31%)	16 (43%)
Assessment inadequate	14 (19%)	5 (14%)
Early death	1 (1%)	2 (5%)

^a Age 70 years and older, performance status 0-1. ^b Any age, performance status 2.

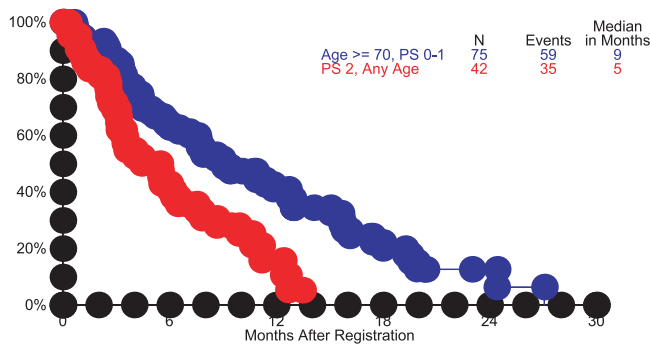


FIGURE 1. Overall survival for the 75 and 42 eligible patients in strata 1 and 2, respectively.

FACT-L TOI score of 49.0 at baseline was 8 points lower (worse) than the stratum 1 mean FACT-L TOI score of 57.1. This same level of difference was present at week 22. The negative slope shown in Figure 2 represents deteriorating FACT-L TOI scores over the 22 week-period, with a steeper slope observed for stratum 2. The mean differences between weeks 0 and 22 were very similar for patients in the two strata, -3.6 for patients in stratum 1 and -3.3 for patients in stratum 2.

DISCUSSION

This is the first prospective clinical trial conducted by the Southwest Oncology Group targeting patients with advanced stage NSCLC age 70 years and older or with a PS of 2. Sequential vinorelbine and docetaxel was a well-tolerated treatment in both patient strata.

Patients age 70 years and older with a good PS (0-1) had an improved survival compared with the PS 2 cohort. The

median survival of 9.1 months in good PS elderly patients is comparable with the survival noted with single-agent vinorelbine in the ELVIS trial and single-agent vinorelbine or gemcitabine in the MILES trial.^{10,12} In addition, survival compares favorably with the results obtained in randomized trials with platinum-based combination chemotherapy for patients of any age.³⁵⁻³⁷

A number of reports have suggested that further prognostic information can be attained by carefully recording, in addition to PS, the extent of comorbidity.³⁸⁻⁴⁰ Within the cohort of patients age 70 years and older with a good PS, we noted that increasing comorbidity was associated with shortened survival, although the difference did not reach statistical significance. Conversely, in the PS 2 stratum, a trend for better survival with increasing comorbidity was noted. This counterintuitive finding was not due to a predominance of younger patients in the PS 2 stratum, but more likely represents an unstable finding based on the small sample size of this stratum. Alternatively, there may be a cohort of patients whose PS 2 status is based on stable comorbidities that are not cancer related. This group may have an intrinsically better prognosis than patients who have a PS of 2 that is directly related to the underlying cancer. We recommend careful assessment of comorbidity as an essential component of future prospective trials in these subsets of advanced stage NSCLC. In addition, for patients with a PS of 2, it might be useful to define whether the impaired PS is primarily related to the underlying cancer or stable comorbidities.

Previous reports in advanced NSCLC have noted improvements in patient-reported quality of life (particularly symptom status) with chemotherapy treatment.^{10,41,42} Not unexpectedly, the strongest finding of the current trial regarding patient-reported outcomes was that patients with poorer

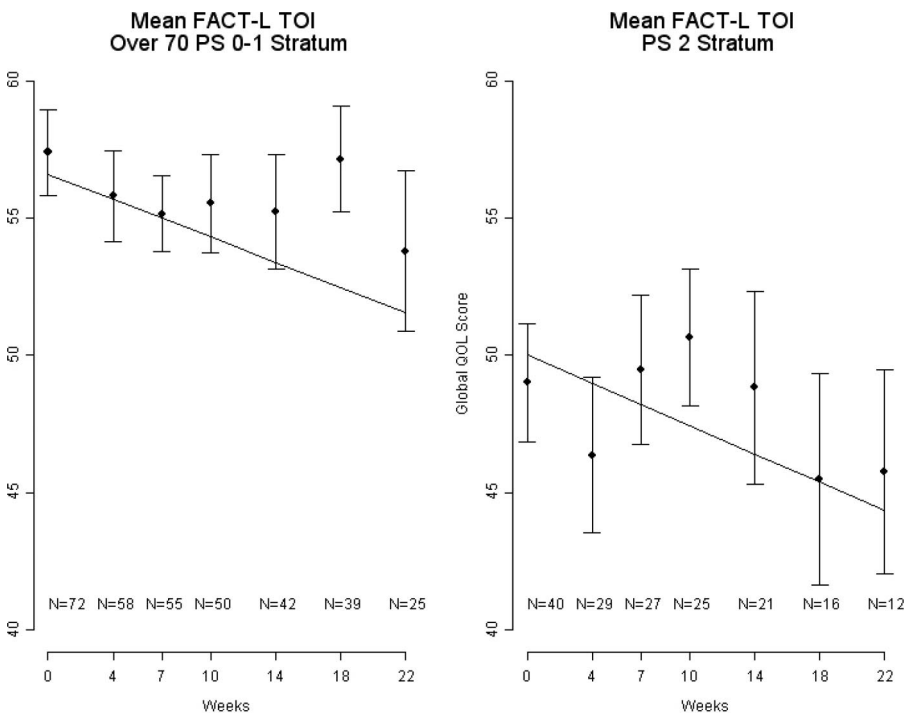


FIGURE 2. Functional Assessment of Cancer Therapy–Lung Outcome Index (TOI) scores by stratum: stratum 1 (performance status = 0 or 1, age 70 and older); stratum 2 (performance status = 2, any age). The mean FACT-L TOI score with standard error bars at each time point (●). The solid line indicates the regression line from a longitudinal mixed effects model of FACT-L TOI scores over time. The sample size at each time point is provided. QOL, quality of life.

baseline performance status reported a worse functional status (FACT-L TOI score) than did patients with better baseline PS; this pattern was also observed at the end of the second treatment period. In both cases, differences of 8 points were observed favoring patients with better PS. Differences of ≥ 5 points have been shown to be clinically significant for the FACT-L TOI.³² A general trend for deterioration in scores over the 22-week treatment period was noted in both strata. However, the mean score differences at 22 weeks of 3.6 and 3.3 in strata 1 and 2, respectively, would not be regarded as clinically significant. It is difficult to attribute change in FACT-L TOI scores to either time (expected deterioration over time in advanced stage disease) or to the addition of a second treatment because the study design confounds these two variables. In addition, these preliminary results may not adequately reflect the impact of missing data on estimates of change in functional status; additional analyses are currently underway to examine more thoroughly potential biases associated with missing data.

At present, it is clear from prospective trials that patients older than the age of 70 with advanced stage NSCLC and a good PS will achieve substantial benefit with single-agent chemotherapy using an active modern agent such as vinorelbine and gemcitabine. Our results, albeit in a phase II trial, suggest that sequential use of vinorelbine and docetaxel is another viable option for these patients. The potential advantage of additional concurrent agents is unclear. Retrospective subset analyses from a number of phase III trials suggest superiority for combination platinum-based therapy compared with single agents in both younger and older patients.^{8,9} Prospective trials are needed, however, to establish whether platinum-based combination therapy is associated with improved survival and acceptable toxicity compared with single-agent chemotherapy in elderly patients with a good PS.

The large proportion of patients with advanced stage NSCLC and a PS of 2 remains a significant therapeutic challenge. The value of chemotherapy in this cohort of patients has never been demonstrated in a prospective trial compared with supportive care alone. In the ELVIS trial comparing vinorelbine with best supportive care in patients age 70 years and older, a small proportion of patients had a PS of 2. Analysis of survival in this subset of patients suggests value for active treatment.¹⁷ Median survival was 26 weeks and 8 weeks in the cohort of patients receiving vinorelbine and best supportive care, respectively. As is the situation with elderly patients with a good PS, the potential value of combination chemotherapy in PS 2 patients has never been definitively proven. Retrospective analyses of phase III trials of platinum-based therapy in advanced NSCLC have consistently shown median survival for PS 2 patients of ≤ 4 months.^{9,43,44} In addition, many of these trials have shown enhanced toxicity in PS 2 patients.^{15,45} A recent example is ECOG (Eastern Clinical Oncology Group) 1594, a comparison of four modern platinum-based doublets.³⁷ Study entry criteria initially included PS 2. However, accrual to this cohort was suspended after an interim analysis reported excessive toxicity. Although a subsequent analysis

suggested that most deaths in the PS 2 population were not treatment related, significant grade 3/4 toxicities were noted. Grade 3/4 neutropenia ranged between 47% and 60% for the four study arms. Most importantly, median survival was only 4.1 months. Retrospective analysis of another recent phase III trial suggests possible superiority for combination compared with single-agent chemotherapy. Cancer and Leukemia Group B (CALGB) trial 9730 was a phase III study comparing paclitaxel with the combination of carboplatin/paclitaxel.⁹ Eighteen percent of patients enrolled had a PS of 2. Analysis of outcome in this group revealed a longer median survival (4.7 months versus 2.4 months) in the group receiving combination versus single-agent therapy.

Our experience with sequential vinorelbine and docetaxel in PS 2 patients compares favorably with the ECOG and CALGB trials. The study regimen was tolerable and resulted in a promising median survival of 5.5 months. Two other prospective trials targeting exclusively PS 2 patients with advanced NSCLC have recently been reported in preliminary form.^{45,46} The Hellenic Cooperative Oncology Group compared gemcitabine with a combination of gemcitabine and carboplatin. Median survival was 4.8 and 6.7 months on the single-agent and combination arms, respectively ($p = 0.49$).⁴⁵ ECOG, attempting to build on their experience from ECOG 1594, performed a randomized phase II trial (ECOG 1599) randomizing patients to receive either paclitaxel/carboplatin or gemcitabine/cisplatin, each given at attenuated doses. Hematologic toxicity was reduced with the lower chemotherapy doses compared with the ECOG 1594 historical control and median survival was 6.1 and 6.8 months on the paclitaxel/carboplatin and gemcitabine/cisplatin arms, respectively.⁴⁶

Unresolved issues for future prospective trials in PS 2 patients include definitive comparisons of combination versus single-agent chemotherapy, determining the potential role of new molecular-targeted agents and more precise identification of the PS 2 population, incorporating comorbidity assessments. In addition, it is critically important to carefully assess symptom status in this patient population. A number of previous studies have suggested symptom improvement even in the absence of clear-cut survival improvement in PS 2 patients.^{47–50} The Southwest Oncology Group is currently conducting a trial of single-agent erlotinib alone in previously untreated patients with a PS of 2 with this objective in place.

In conclusion, a regimen of sequential vinorelbine and docetaxel is well tolerated and effective in comparison with reports of other regimens tested in patients with advanced NSCLC age 70 years and older and/or with a PS of 2. Elderly patients with a good PS have improved survival compared with PS 2 patients receiving this regimen. Survival in the PS 2 stratum compares favorably with the results with previous platinum-based regimens, although alternative approaches clearly are needed for this patient population.

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