

The 800-lb Gorilla We All Ignore: Treatment of NSCLC in Elderly and PS 2 Patients

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Abstract: Patients with non-small cell lung cancer (NSCLC) typically have advanced disease on presentation. First-line palliative platinum-based doublet chemotherapy has emerged as the standard of care in fit, younger patients. However, patients with advanced age and/or impaired performance status have been relatively underrepresented in clinical trials. Retrospective analyses and the few existing prospective randomized trials in these populations have suggested a poorer overall prognosis, yet also provide evidence of benefit from systemic therapy. Toxicity is generally manageable, and in most cases, comparable to that of younger, healthier patients. There are clearly expanding roles for nonplatinum chemotherapy agents and newer targeted therapies, which have generally yielded decreased toxicity compared to platinum-based chemotherapy without sacrificing efficacy. Appropriate pretreatment assessment and proper patient selection is of paramount importance; it is imperative to treat patients who are most likely to garner benefit. In summary, data suggest that these relatively neglected populations of NSCLC patients can be safely treated, and can benefit from palliative systemic therapy. Single-agent chemotherapy is generally recommended over combination chemotherapy, although investigation of newer targeted therapies or alternative agents may allow for combination therapy in the near future. Further prospective investigation is absolutely warranted.

Background

Lung cancer remains a formidable challenge in 2007. Over 186,000 patients are diagnosed annually (12% of all new US cancer cases) and approximately 167,000 die of the disease (28% of US cancer mortalities).¹ Whereas lung cancer is the third most common type of cancer, it is the leading cause of cancer mortality; non-small cell lung cancer (NSCLC) accounts for the majority (85%) of cases.¹ Worldwide, NSCLC annually accounts for 1.2 million new cancer cases, and 1.1 million cancer deaths.² Few data³⁻⁵ support screening asymptomatic patients for early-stage NSCLC; consequently, only 20% of new patients present with localized disease (40% regional and 40% metastatic disease¹). The 5-year survival rate for a newly diagnosed NSCLC patients (~15%) has not improved over the past 80 years,¹ despite advances in diagnosis, stag-

Keywords

Nonsmall cell lung cancer (NSCLC), impaired performance status (PS 2), elderly, geriatric oncology, chemotherapy, targeted therapy

ing, and treatment. Contributing to this dismal prognosis is the difficulty of curing early-stage disease, relative to patients with stage-matched cancers of other body sites. Stage-specific 5-year survival rates (as of the late 1990s) have been reported to be 38–61% (clinical stages Ia–Ib), 22–34% (IIa–IIb), 9–13% (clinical stage IIIa), and 1–7% (clinical stage IIIb–IV).⁶ The recently demonstrated survival advantage of adjuvant chemotherapy^{7–11} may increase survival rates somewhat. Given the tendency for NSCLC patients to present with advanced disease, and the limited success of modern treatments for early-stage lesions, palliative systemic therapies remain the standard treatment for most NSCLC patients. In this setting, first-line platinum-based doublet chemotherapy has provided a modest survival advantage over best supportive care,¹² and the role of nonplatinum doublets has also been explored.^{13–16} Response rates remain 30% at best and are not typically durable.¹⁴ However, the quality of best supportive care (antiemetics, analgesia, growth factors, etc.) has improved in recent years, allowing more patients, and relatively sicker patients, to consider systemic therapy.

The investigation of elderly (>65 years of age) and poor performance status (PS) patients (PS 2 by Eastern Cooperative Oncology Group [ECOG], 50–60% by Karnofsky scale) has recently emerged as an essential aspect of NSCLC research. The median age at diagnosis for those with lung cancer is 69 years,¹⁷ suggesting that the prevalence of NSCLC will increase as the population ages. Of importance is the relative decrease in incidence and mortality over the past 15 years in patients under 50 years old, whereas patients over 70 years old have experienced the opposite trend.¹⁸ Unfortunately, elderly patients have been relatively underrepresented in clinical trials.^{19,20} Considerable hesitation exists on the part of clinicians and investigators to treat elderly and younger patients with equally aggressive therapy, particularly in the palliative setting, because physiologic alterations and comorbidities in the elderly often increase the risks of treatment. However, data indicate that fit elderly patients (PS 0–1) achieve similar response and survival as younger patients, with minimal increases in toxicity.^{12,21} Moreover, improvements in supportive care have facilitated aggressive treatment of disease-related symptoms and treatment-related toxicities in such patients. Similarly, patients with poor performance status (ie, PS 2), regardless of age, are more likely to suffer toxicity than patients with better PS and may not reap equivalent benefit from therapy. Historically, this has led to evaluation of elderly and poor-PS patients together, as one poor-prognosis group with potentially higher therapy-related risk than benefit. However, there are very clear differences between the two populations, and therapeutic distinctions exist for each group; as always, proper patient selection is of

paramount importance. There are a number of relevant prospective clinical trials and retrospective analyses to review in this regard.

Treatment of NSCLC in the Elderly

Elderly individuals experience very real physiologic changes that may increase both the likelihood and level of toxicity.²² For example, creatinine clearance is often significantly impaired, which can preclude use of some systemic therapies (eg, cisplatin) and may exclude older patients from clinical trials investigating new compounds. The cardiac, nervous, integumentary, and hematopoietic systems also become more fragile with age, predisposing elderly patients to specific toxicities.

The National Comprehensive Cancer Network and the American Society of Clinical Oncology have published guidelines to optimize treatment for elderly patients.^{23,24} Recommendations include a comprehensive geriatric assessment to better define prognosis and predict tolerance to treatment (see Table 1), dose adjustments for renal dysfunction, prophylactic use of erythropoietic (to maintain hemoglobin ≥ 12 g/dL) and granulocytic growth factors (based on regimen used), and avoidance of substantially toxic therapies. The ultimate goals of this assessment are to estimate life expectancy, to assess functional reserve, and to identify and treat reversible conditions that may cloud further assessment or prohibit treatment. For example, symptomatic elderly patients receiving palliative therapy are likely to develop depression and thus warrant aggressive psychosocial intervention.²⁵ Included in any pretreatment assessment should be a frank discussion between patient and provider regarding the goals of treatment, the likelihood of attaining them, and the level of anticipated toxicity to do so. This prognostic approach has already been validated, even in patients with good PS.²⁶

Other useful assessment tools are available, such as the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30),²⁷ the Vulnerable Elders Survey,²⁸ and Cardiovascular Health Study methods²⁹ (Table 1). Lung cancer-specific surveys,^{30,31} such as the Functional Assessment of Cancer Therapy–Lung, the Lung Cancer Symptom Survey, or the EORTC QLQ Lung Cancer Module (QLQ-LC13), examine multiple patient-reported factors, and may be of additional value. To further illustrate the importance of such subjective measures, elderly NSCLC patients are more likely to accept second-line chemotherapy if symptomatic improvement is to be expected, in addition to any survival benefit.³² Moreover, the US Food and Drug Administration (FDA) has strongly encouraged that quality of life (QoL) or other patient-reported outcomes be included, with survival, as endpoints in clinical trials.³³

Table 1. Feasible, Reliable, and Valid Pretreatment Assessment Tools

Screening Instrument	Description
Comprehensive Geriatric Assessment (CGA) ³⁰	Examines in detail cognitive, emotional, nutritional, socioeconomic, and physical status, ability to function in daily life, and presence/absence of polypharmacy or specific geriatric syndromes (eg, dementia, neglect, falls, etc.)
Vulnerable Elders Survey ²⁸	After answering 13 simple questions, patients are scored; any patient with score >4 would benefit from a CGA
Cardiovascular Health Study methods ²⁹	Examines self-reported exhaustion, unintentional weight loss, weakness, walking speed, and level of physical activity, and then groups patients into three categories: fit, prefrail, or frail
EORTC QLQ-30 ²⁷ and -LC13 ³⁰	Brief 30-item questionnaire, self-reported overall quality of life, with 13-item subscale specific to lung cancer
Functional Assessment of Cancer Therapy–Lung (FACT-L) ³¹	36-item survey of general health questions, and lung cancer–specific questions; extremely informative and flexible
Lung Cancer Symptom Survey (LCSS) ³¹	Specifically measures symptoms and subsequent distress as distinct entities in 9-item format; shortest/quickest of all questionnaires; unique in inclusion of clinician in 6 other items

EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = Core Quality of Life Questionnaire; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer Module.

Single-agent Chemotherapy in NSCLC Patients

Multiple trials in NSCLC have identified higher rates of toxicity with combination chemotherapy regimens compared to single agents; as such, the latter was one of the first approaches investigated in elderly individuals. The most frequently evaluated agents are third-generation and include vinorelbine (Navelbine, Bristol-Myers Squibb), gemcitabine (Gemzar, Eli Lilly), paclitaxel (Taxol, Bristol-Myers Squibb), and docetaxel (Taxotere, Sanofi-Aventis), although newer agents, such as pemetrexed (Alimta, Eli Lilly), are becoming more popular, both in clinical trials and in clinical practice (Tables 2, 3, and 4).

Vinorelbine (VNR) has shown encouraging results for elderly patients in the first-line setting (Tables 2 and 3). Initial phase II trials demonstrated reproducibly reasonable response rates and survival times, leading to the subsequent phase III ELVIS trial⁴¹; ultimately, this trial became the first prospective study to demonstrate a clear treatment benefit in the elderly population. Patients with advanced NSCLC (stage IIIB/IV), ECOG PS 0–2, and age over 70 years were randomized to receive either best supportive care or the same plus first-line VNR. Accrual progressively declined, leading to early termination of the trial, hypothesized by many to be a result of referring practitioner preferences toward the treatment arm, as patients successfully continued treatment on study. Eighty percent of patients were PS 0–1. VNR-treated patients experienced better quality of life by EORTC scales (QLQ-C30 and

QLQ-LC13), reduced cancer-related symptomatology (eg, fatigue, cough, etc.) and acceptable toxic symptoms (albeit slightly higher rates of gastrointestinal distress, alopecia, and neuropathy in the VNR arm). Median survival, 6-month survival, and 12-month survival significantly favored the VNR arm. Phase II data^{42–44} also suggest a first-line role for oral VNR in elderly patients, with no clear need for routine dose reduction based on age alone⁴⁵; however, second-line activity of oral VNR is somewhat debatable.⁴⁶ In a recent retrospective evaluation of salvage VNR (in second- through fifth-line settings), elderly patients achieved better survival than their younger counterparts, with similar rates of toxicity.⁴⁷

Other cytotoxic agents have also been evaluated. Retrospective review of phase II trials evaluating paclitaxel every 3 weeks in elderly patients has revealed no significant differences in efficacy, and similar toxicity, aside from a preponderance of neutropenia in the elderly.⁴⁸ Weekly paclitaxel has proved more tolerable, with no clear decrement in efficacy (Table 2). Phase II trials of docetaxel have provided definitive evidence of activity (Table 2). There are conflicting data regarding the chance of serious myelosuppression, but there is consensus that a weekly schedule is the best tolerated. A recent phase III randomized study⁴⁹ (Table 3) compared VNR and docetaxel in 182 elderly patients with stage IIIB–IV NSCLC, and demonstrated clear superiority of docetaxel over VNR in efficacy (response rate [RR] 22.7% vs 9.9%; median survival time [MST] 13.9 vs 9.9 months; 1-year overall survival [OS] 59.2% vs 36.5%) as well as QoL

Table 2. Selected Prospective Phase II Trials of Single-agent First-line Chemotherapy in Elderly NSCLC Patients

First Author	Number of Patients (Age, years)	Drug/Dose	RR	Median OS, Months
Gridelli ³⁴	43 (>70)	VNR 30 mg/m ² weekly	23%	8.3
Martoni ³⁵	46 (>70)	Gem 1000 mg/m ² d1+8+15 q4 wk	22%	9
DeMaio ³⁶	51 (half >75)	FDR Gem 10 mg/m ² /min	17.6%	~10 (41 wks; median PFS 16 wks)
Fidias ³⁷	35 (>70)	Pac 90 mg/m ² weekly × 6, q8 wk	23%	10.3
Garbo ³⁸	60 (>70)	Pac 80 mg/m ² d1+8+15 q4 wk	3.3%	8.2
Lilenbaum ³⁹	96 (>70) 84 elderly 72 PS-2	Doce 75 mg/m ² q3 wk or Doce 30 mg/m ² d1+8+15 q4 wk	15% (all pts)	NR
Takigawa ⁴⁰	35 (>75)	Doce 60 mg/m ² q3–4 wk	40%	15.6

Doce = docetaxel; FDR = fixed-dose-rate; Gem = gemcitabine; NSCLC = non-small-cell lung cancer; NR = not reported; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; PS = performance status; PTS = patients; RR = response rate; VNR = vinorelbine.

Table 3. Prospective Randomized Phase III Trials of Single-agent First-line Chemotherapy in Elderly NSCLC Patients

First Author/Trial	Number of Patients (Age, years)	Drug/Dose	RR	Survival
Gridelli ⁴¹ (ELVIS)	154 (>70)	VNR 30 mg/m ² d1 + 8 q3 wk + BSC (vs BSC alone)	19.7%	Median OS 28 vs 21 wks (<i>P</i> = .03) 1-yr OS 32% vs 14% (<i>P</i> = NR) HR 0.65 (95% CI = 0.45–0.93)
Takeda ⁴⁹	182 (median 76)	Doce 60 mg/m ² q3 wk × 4 vs VNR 25 mg/m ² d1 + 8 q3 wk × 4	22.7% 9.9% (<i>P</i> = .019)	MST 13.9 mos; 1-yr OS 59.2% MST 9.9 mos; 1-yr OS 36.5% (<i>P</i> = .038)

BSC = best supportive care; CI = confidence interval; Doce = docetaxel; ELVIS = Elderly Lung cancer Vinorelbine Italian Study; HR = hazard ratio; MST = median survival time; NSCLC = nonsmall cell lung cancer; NR = not reported; OS = overall survival; RR = response rate; VNR = vinorelbine.

(of 8 disease-related symptoms, appetite and fatigue were significantly improved). Overall toxicity was mild in each arm; however, serious neutropenia was more common in docetaxel-treated patients (83% vs 69.2%; *P* = .031). Gemcitabine (GEM) has demonstrated activity in a retrospective analysis,⁵⁰ with no appreciable decrement in efficacy for elderly patients; this has been validated in dedicated phase II trials in elderly NSCLC patients (Table 2), with manageable toxicity. However, there have been no randomized trials of GEM versus best supportive care in the elderly population.

Sequential single-agent therapy may enable patients to avoid the toxicity of combination chemotherapy, while

harnessing potential efficacy advantages of non-cross-reacting agents (Table 4). In trials evaluating this approach, patients were scheduled to receive the second agent, regardless of response to the first agent. Hesketh and associates⁵¹ evaluated sequential vinorelbine and docetaxel in elderly and PS 2 patients. Of 75 elderly patients with good PS (0–1) enrolled in this trial, the approach proved reasonably efficacious and tolerable, and outcomes were far better than those of the 44 PS 2, but younger, patients (median OS 9 months in elderly vs 5 months in PS 2). Recently, Gridelli and colleagues performed a randomized phase II trial⁵² comparing single-agent pemetrexed to the sequential administration of pemetrexed and GEM. In a

Table 4. Prospective Phase II Trials of First-line Sequential Single-agent Chemotherapy in Elderly NSCLC Patients

First Author	Number of Patients (Age, years)	Drug/Dose	RR	Survival
Hesketh ⁵¹ (SWOG)	119 (75 pts >65, w/PS 0–1; 44 pts PS 2)	VNR 25 mg/m ² d1+8 q3 wk × 3, immediately followed by Doce 35 mg/m ² d1+8+15 q4 wk × 3	Elderly: 21% PS 2: 10%	Elderly: Median OS 9 months Median PFS 5 months 1-yr OS 35% PS 2: MST 4 months Median PFS 3 months 1-yr OS 14%
Gridelli ⁵² (randomized)	92	Pem 500 mg/m ² q3 wk × 8 vs Pem 500 mg/m ² q3wk × 2, then Gem 1200 mg/m ² d1+8 q3 wk × 2 (then repeat again)	12.5% vs 12.2%	Pending
Latreille ⁵³	42 (median 75, 50% PS-2)	VNR 30 mg/m ² d1+8 q3 wks (× 2 for SD, or × 1 after best response), followed by Gem 1000 mg/m ² d1+8 q3 wks (× 2 for SD, or × 1 after best response), followed by either Gem or VNR until PD (per patient preference)	38%	Median OS >6 months Median TTP 3.5 months 1-yr OS >19%
Martoni ⁵⁴	52 (median 76)	Gem 1000 mg/m ² d1+8+15 q4 wks × 3, followed by VNR 25 mg/m ² d1+8+15 q4 wks until PD/intolerance	23%	Median OS 10 months Median TTP 6 months 1-yr OS 42%

Doce = docetaxel; Gem = gemcitabine; MST = median survival time; NSCLC = non-small cell lung cancer; NR = not reported; OS = overall survival; PD = progressive disease; Pem = pemetrexed; PFS = progression-free survival; PS = performance status; pts = patients; RR = response rate; SWOG = Southwest Oncology Group; TTP = time to progression; VNR = vinorelbine.

preliminary analysis, rates of clinical benefit and safety appeared similar; survival analysis is ongoing. Preliminary data from the trial by Latreille and associates,⁵³ and mature data from Martoni and coworkers,⁵⁴ also show encouraging response rates and survival (Table 4).

In second-line trials of single-agent therapy versus best supportive care, docetaxel and erlotinib (Tarceva, OSI/Genentech) have each demonstrated a survival advantage in phase III trials that happened to include elderly patients.^{55,56} In a similar patient population, Hanna and coauthors have prospectively demonstrated non-inferiority and decreased toxicity for second-line pemetrexed compared to docetaxel.⁵⁷ A recent retrospective subset analysis⁵⁸ of the Hanna trial demonstrated no clear differences between the 86 elderly (>70 years) patients and the 485 younger patients with regard to

efficacy; 1- and 2-year survival rates were similar, as were response rates. Pemetrexed proved safer, however, with significantly lower rates of febrile neutropenia (2.5% vs 19%, $P=.025$) and less frequent treatment withdrawal for toxicity. A trend toward superior time to progression (TTP) and OS was observed, favoring pemetrexed in the elderly (9.5 vs 7.7 months).

Combination Chemotherapy in Elderly NSCLC Patients

Platinum-based doublet chemotherapy provides untreated NSCLC patients a modest but true survival advantage over best supportive care; this was confirmed in a landmark meta-analysis, and no age-related differences were noted.¹² Given its efficacy in controlling or alleviating symptoms,

and in globally improving QoL, this approach has largely become the standard of care in most NSCLC patients. However, cisplatin (CDDP)-based therapy can be very toxic, particularly to the renal, hematopoietic, and nervous systems; given the particular susceptibility of the elderly to these toxicities, understandable apprehension exists in employing this combination in older patients. Additionally, the need for aggressive intravenous fluid administration with CDDP can be problematic in elderly patients, a population generally at higher risk for cardiac disease and fluid overload. Nonplatinum combinations have been evaluated as a result; thus, there are both platinum-based and nonplatinum-based combinations to consider.

Platinum-based Doublets

There has been no prospective randomized phase III study performed to date, exclusively exploring the true risk/benefit ratio of first-line platinum-based doublets in the elderly NSCLC population. However, a retrospective multicenter analysis⁵⁹ suggested a statistically significant association between increasing age and likelihood of death within 30 days of starting such therapy. In contrast, retrospective review of trials evaluating platinum-based chemotherapy that allowed elderly patients to enroll (total ~20% of all patients), have not shown significant differences between elderly and younger patient populations in rates of response, survival, or QoL (Table 5), although toxicity tended to be worse. Age was not predictive of response to chemotherapy or survival in another retrospective evaluation⁶⁰ of 477 CDDP-treated NSCLC patients (median age 60, oldest age 78); in contrast, sex, stage and ECOG PS were found to be predictive in multivariate analysis. Nevertheless, one clear area of consensus is the need for prospective data in this patient population.

Retrospective analysis of ECOG 5592 demonstrated no significant differences between younger and older patients with respect to efficacy or toxicity, although leukopenia and neuropsychiatric problems were slightly more likely in the elderly cohort.⁶² Patients over 75 years old experienced more leukopenia than patients aged 70–75 years ($P=.06$). A retrospective analysis⁶⁶ of elderly patients enrolled in two Southwest Oncology Group (SWOG) trials also demonstrated no significant difference in survival (8.6 vs 6.9 months; $P=.06$), TTP (4.2 vs 3.9 months; $P=.62$), or overall toxicity; however, elderly patients were more likely to discontinue CDDP/VNR (46%) than carboplatin/paclitaxel (CBP/PAC; 16%). Interestingly, subset analysis of patients over 65 years old in the TAX-326 trial⁶⁴ demonstrated superior efficacy of CDDP/docetaxel (DOCE) over CDDP/VNR (1-year OS 52% vs 41%; 2-year OS 24% vs 17%) in this population. Toxicity was less prevalent in those patients receiving CBP.

The phase III ECOG 1594 trial⁷⁰ randomized over 1200 patients (20% of whom were ≥ 70 years old) to receive GEM/CDDP, DOCE/CDDP, or PAC/CBP, compared to PAC/CDDP. Retrospective analysis⁶⁵ of demographic differences demonstrated only a higher chance of cardiopulmonary comorbidities in the elderly. Response and survival were not significantly different between the two age groups, and the elderly experienced only a slight increase in serious toxicity ($P=.04$). Of the 9 patients over 80 years old, none was able to complete all six cycles of treatment (and only 1 completed 4 cycles); indeed, median survival was only 4.2 months, regardless of PS. In contrast, another retrospective review⁷¹ of 82 patients over 80 years old found that 38 (46%) were able to receive chemotherapy, and that systemic treatment (predominantly CBP/VNR) given every 4 weeks produced a superior median survival (28.3 vs 8.5 weeks) compared to best supportive care alone.

A Cancer and Leukemia Group B phase III trial⁷² (CALGB 9730) comparing PAC/CBP to PAC demonstrated significantly higher response rates (30% vs 17%, $P<.0001$) and longer MST (8.8 vs 6.7 months, $P=.25$) in the doublet arm. There were no appreciable survival differences between the elderly (≥ 70 years) and nonelderly populations; moreover, a trend toward improved survival from platinum-doublet therapy was observed in the elderly cohort (8.0 vs 5.8 months), albeit without sufficient power to achieve statistical significance.

In an effort to lessen CDDP-related toxicity, some investigators have prospectively evaluated CDDP-based regimens of third-generation agents on a more frequent, lower-dose schedule with some success (Table 6). Another popular strategy has been substitution of CBP for CDDP, which significantly limits the gastrointestinal, renal, neurologic and cardiac concerns in elderly patients, but may produce slightly more hematologic toxicity. A recent retrospective analysis⁷³ of a phase III trial⁷⁴ comparing CBP/PAC every 3 weeks to weekly PAC/monthly CBP reported a trend toward superior efficacy with the weekly PAC regimen in patients aged at least 70 years (overall response rate [ORR] 26% vs 19%; MST 37.1 vs 31.1 weeks). A retrospective subset analysis of another randomized phase II trial exploring the optimal scheduling of GEM/CBP demonstrated similar rates of response (43.3% elderly vs 28%), TTP (5.3 vs 4.2 months), median survival (10.2 vs 7.8 months), and toxicity between the elderly and nonelderly populations.⁷⁵ Finally, oxaliplatin has been substituted for either CDDP or CBP, with some promise in early studies.

Ongoing trials of platinum-based chemotherapy doublets in elderly NSCLC patients include a phase III effort in patients aged at least 70 years through the Japan Cooperative Oncology Group (JCOG 0207), comparing weekly DOCE with or without weekly CDDP.

Table 5. Retrospective Subset Analyses of Elderly and/or PS-2 NSCLC Patients in Randomized Phase III Trials Evaluating Platinum-based First-line Doublet Chemotherapy

Study	Number of Elderly Patients (of total)	Platinum Agent Dose and Chemotherapy Regimen	RR of Elderly Patients (vs nonelderly)	Survival of Elderly [‡] (vs nonelderly)
HOG ⁶¹	53 elderly (260)	CDDP 100 mg/m ² (+ Gem)	15% (29%)	OS: 7.7 vs 9.4 mos 1-yr OS: NR
ECOG 5592 ⁶²	86 elderly (574)	CDDP 75 mg/m ² (+ either VP-16 or Pac)	23.3% (21.5%)	OS: 8.5 vs 9.1 mos 1-yr OS: 29% vs 38%
CALGB 9730 ⁶³	77 elderly (284)	Cbp AUC 6 (+ Pac)	Elderly: 36% (30%) PS-2: 24% (10%)	Elderly: OS: 8.0 vs 8.5 mos 1-yr OS: 35% vs 36% PS-2: OS: 4.7 vs 2.4 mos (<i>P</i> =.016) 1-yr OS: 18% vs 10%
TAX-326 ⁶⁴	*149 (259) *134 (270) *118 (288)	CDDP 75 mg/m ² (+ Doce) CDDP 100 mg/m ² (+ VNR) Cbp AUC 6 (+ Doce)	NR (32%) NR (25%) NR (24%)	OS: 12.6 vs 11.3 mos [†] 1-yr OS: 52 vs 46% [†] OS: 9.9 vs 10.1 mos [†] 1-yr OS: 41 vs 41% [†] OS: 9.0 vs 9.4 mos [†] 1-yr OS: 38 vs 38% [†]
ECOG 1594 ⁶⁵	227 elderly (1139)	CDDP 75–100 mg/m ² (+ Pac or Doce or Gem) or Cbp AUC 6 (+ Pac)	Elderly: 25% (22%)	Elderly: OS: 8.3 vs 8.2 mos 1-yr OS: 33% vs 35% PS-2: OS: 4.1 mos (all arms) 1-yr OS: 19% (all arms)
SWOG 9509/9308 ⁶⁶	117 elderly (608)	CDDP 100 mg/m ² (+VNR) or Cbp AUC 6 (+ Pac)	NR (NR)	OS: 6.9 vs 8.6 mos 1-yr OS: 30% vs 40%
LCCC 9719 ⁶⁷	67 elderly (230)	Cbp AUC 6 (+ Pac)	27% (20%)	OS: 7.1 vs 7.8 mos 1-yr OS: 33% vs 30%
CALGB 8931 ⁶⁸	31 elderly (253)	CDDP 100 mg/m ² (+ VNB)	16% (31%)	OS: 5.7 vs 8.0 mos 1-yr OS: 30% vs 27%
FACS ⁶⁹	105 elderly (602)	CDDP 80 mg/m ² (+ CPT-11) vs Cbp AUC 6 (+ Pac) or CDDP 80 mg/m ² (+ Gem or VNR)	26% 20% 32%, 50%	1-yr OS: 48% [‡] 1-yr OS: 48% [‡] 1-yr OS: 61%, 46% [‡] (OS: NR)

*>65 years old.

[†]Entire cohort.

[‡]Differences are not statistically-significant.

AUC = area under curve; CALGB = Cancer and Leukemia Group B; Cbp = carboplatin; CDDP = cisplatin; CPT-11 = irinotecan; Doce = docetaxel; ECOG = Eastern Cooperative Oncology Group; FACS = Four-Arm Cooperative Study; Gem = gemcitabine; HOG = Hoosier Oncology Group; LCCC = Lineberger Comprehensive Cancer Center; mos = months; NSCLC = non-small cell lung cancer; NR = not reported; OS= overall survival; Pac = paclitaxel; PFS = progression-free survival; RR = response rate; SWOG = Southwest Oncology Group; VNB = vinblastine; VNR = vinorelbine; VP-16 = etoposide.

Table 6. Selected Prospective Phase II Trials of Platinum-based First-line Chemotherapy Doublets in Elderly NSCLC Patients

First Author/Trial	Number of Patients (Age, years)	Drug/Dose	RR	Survival
Inoue ⁷⁶	42 (>70)	Cbp AUC 6 + Pac 70 mg/m ² d1+8+15 (q4 wks)	45%	MST: 14 mos 1-yr OS: 62%
Giorgio ⁷⁷	40 (>70)	Cbp AUC 5 + Pac 175 mg/m ² (q3 wks)	25%	Median OS: 7.8 mos 1-yr OS: 18% Median TTP: 4 mos
Ohe ⁷⁸	33 (≥ 75)	CDDP 25 mg/m ² + Doce 20 mg/m ² (weekly × 3, q4 wks)	52%	MST: 15.8 mos
Takatani ⁷⁹	40 (>75)	Cbp AUC 4 + VNR 20 mg/m ² d1+8 (q4 wks)	13.5%	MST: 392d (-14 mos) Median TTP: 114d (-4 mos)
Martins ⁸⁰	44 (>70)	CDDP 60–90 mg/m ² + VNR 25 mg/m ² d1+8 (q3 wks)	54%	MST: 7.2 mos
Feliu ⁸¹	46 (≥ 70)	CDDP 50 mg/m ² + Gem 1000 mg/m ² (q3 wks)	35%	MST: 10.2 mos
Buosi ⁸²	14 (median 73)	Oxali 65 mg/m ² + Gem 1000mg/m ² d1+8 (q3 wks)	43%	NR
MILES-2P ⁸³ (randomized)	159 (45% > 75)	CDDP 60 mg/m ² + Gem 1000 mg/m ² d1+8 (q3 wks) vs CDDP 40 mg/m ² + VNR 25 mg/m ² d1+8 (q3 wks)	43% 36%	MPFS: 25 weeks MOS: 44 weeks MPFS: 21 weeks MOS: 33 weeks

AUC = area under the curve; Cbp = carboplatin; CDDP = cisplatin; Doce = docetaxel; Gem = gemcitabine; MOS = median overall survival; MPFS = median progression-free survival; MST = median survival time; NSCLC = nonsmall cell lung cancer; NR = not reported; OS = overall survival; Oxali = oxaliplatin; Pac = paclitaxel; PFS = progression-free survival; RR = response rate; TTP = time to progression; VNR = vinorelbine.

Nonplatinum-based Doublets

Nonplatinum doublets, in particular GEM/VNR, have also been evaluated and may serve a role in this patient population. Initial phase II studies (Table 7) demonstrated feasibility, safety, and reasonable efficacy in elderly patients.

Randomized phase III trials (Table 8) include the Multicenter Italian Lung Cancer in the Elderly (MILES) trial,⁹⁰ which compared the combination of first-line VNR/GEM to either agent alone in elderly patients (median age 74 years) with advanced NSCLC. Median survival was similar in the two single-agent arms (although not intended to be formally compared); moreover, the combination arm did not significantly improve outcomes, and added substantial toxicity. In a retrospective evaluation,⁹¹ pretreatment QoL and instrumental activities of daily life (ADL) scores were found to be prognostic, whereas Charlson comorbidity and simple ADL scales were not. A phase III randomized study⁹² by the Southern Italy Cooperative Oncology Group demonstrated a sur-

vival advantage for GEM/VNR over single-agent VNR (in contrast to the MILES study), which led to early closure at interim analysis of efficacy; in addition, QoL and disease-related symptoms were significantly better in the combination arm, despite an increase in treatment-related toxicity. Of note, the observed median survival of only 18 weeks in patients receiving single-agent VNR approached that of best supportive care alone in prior literature⁹³; the relatively higher doses of VNR, as well as the inclusion of more patients with brain metastases than in the ELVIS trial, may account for this dismal outcome. Comella and colleagues,⁹⁴ comparing GEM/PAC or GEM/VNR to single-agent PAC or GEM, demonstrated significantly improved survival in the combination arms, with acceptable levels of treatment-related toxicity. Despite the conflicting results reported by these phase III trials, the largest effort (MILES) has suggested that nonplatinum combinations are probably not superior to their constituent single agents.

Table 7. Prospective Phase II Trials of First-line Non-platinum Chemotherapy Doublets in Elderly NSCLC and/or PS-2 Patients

First Author	Number of Patients (Age, years)	Drug/Dose	RR	Survival
Gridelli ⁸⁴	49 (median 74)	Gem 1000 mg/m ² d1+8 and VNR 25 mg/m ² d1+8 (q3 wks)	18.4%	NR
Feliu ⁸⁵	49 (38 >70)	Gem 1000 mg/m ² d1+8+15 and VNR 25 mg/m ² d1+8+15 (q4 wks)	26%	1-yr OS: 33%; TTP: 16 weeks
LeCaer ⁸⁶ (GFPC 0202) (nonrandomized)	97 (median 76 in single-agent arm, 72 in combination arm)	Doce 30 mg/m ² weekly ×6 or Doce 30 mg/m ² + Gem 900 mg/m ² d1+8, d22+29 (q6 wks)	12.8% 44%	Median OS: 9.2 months Median TTP: 3.8 months Median OS: 15 months Median TTP: 5.4 months
Santo ⁸⁷	44 (median 70, median KPS 60%)	Gem 1000 mg/m ² d1+8 and Vindesine 3 mg/m ² d1+8 (q3 wks)	38.6%	Median OS: 12 months
Blakely ⁸⁸ (preliminary data, planned accrual 40 pts)	29 (median age 71)	Pem 500 mg/m ² + Gem 1500 mg/m ² (q2 wks)	21%	NR
Hainsworth ⁸⁹	64 (>70 or <70 with PS 2)	Doce 30 mg/m ² d1+8+15 and Gem 800 mg/m ² d1+8+15 (q4 wks)	28%	Median OS: 7 months; 1-yr OS: 30%; 2-yr: OS 17%

*Comparing vinorelbine / gemcitabine vs vinorelbine alone.

AS = actuarial survival; Doce = docetaxel; Gem = gemcitabine; KPS = Karnofsky performance status; MST = median survival time; NSCLC = nonsmall cell lung cancer; NR = not reported; OS = overall survival; Pem = pemetrexed; PFS = progression-free survival; Pts = patients; RR = response rate; TTP = time to progression; VNR = vinorelbine

Ongoing trials of nonplatinum chemotherapy combinations in elderly NSCLC patients include a phase III trial by Mainwaring and associates⁹⁵ evaluating weekly DOCE with or without GEM in 214 patients either at least 65 years old or PS 2. Interim safety analysis found that both regimens were well tolerated, although hematologic toxicities were, not surprisingly, significantly higher in the doublet arm ($P=.01$). Santo and associates⁹⁶ are currently conducting a trial of GEM with or without vindesine in elderly or poor-PS NSCLC patients. As of last publication, 107 patients had accrued (planned accrual 120).

Targeted Therapy of NSCLC in the Elderly

The epidermal growth factor receptor (EGFR) is overexpressed in NSCLC, and is generally correlated with poorer outcomes. Recent recognition of its importance in neoplastic signaling⁹⁷ has led to development of therapeutic agents that target this receptor. The first agent to garner extensive commercial experience in NSCLC was the oral small molecule tyrosine-kinase inhibitor (TKI) gefitinib (Iressa, Wyeth), which had demonstrated both safety and efficacy (response, stable disease and symptomatic improvement) in early trials of previously treated NSCLC patients^{98,99}; this led to subsequent conditional FDA approval of this agent. However, the subsequent phase

III ISEL study¹⁰⁰ did not confirm a significant survival benefit over best supportive care; hence, its approval was revoked and this agent is no longer commercially available, except for those still demonstrating benefit from this agent. Around the same time, early data¹⁰¹ demonstrated safety of erlotinib (Tarceva, OSI/Genentech), another oral small-molecule TKI, at 150 mg daily. The phase III BR.21 study⁵⁶ subsequently confirmed a survival advantage conferred by erlotinib over best supportive care. Finally, cetuximab (Erbix, ImClone) is a monoclonal antibody that binds EGFR, and is currently being evaluated in phase II and III studies in NSCLC.

Because gefitinib was the first widely-available anti-EGFR agent, most studies in the elderly have employed this drug (Table 9). Trials evaluating the combination of anti-EGFR TKIs with standard chemotherapy have been conducted in both the total population and the elderly, but results thus far have been generally disappointing (Table 10).

Retrospective subset analyses and prospective studies have generally confirmed activity of single-agent anti-EGFR TKIs in the elderly, with the development of a characteristic anti-EGFR rash correlated with response in some studies.¹⁰⁵ There has been clear evidence of symptomatic improvement and improvement in overall QoL,¹⁰⁸ and rates of response and survival in the elderly

Table 8. Prospective Randomized Phase III Trials of Non-platinum Chemotherapy Doublets in Elderly NSCLC Patients

First Author/Trial	Number of Patients (Age, years)	Drug/Dose	RR (95% CI)	Survival	
MILES ⁹⁰ (Gridelli)	698	Gem 1000 mg/m ² d1+8 and VNR 25 mg/m ² d1+8	21% (16–26)	Survival: HR 1.17 (0.95–1.44); <i>P</i> =.93 TTP: HR 0.95 (0.78–1.16); <i>P</i> =.32	
		vs Gem 1200 mg/m ² d1+8	16% (12–21)	OS 30 wks; TTP 19 wks; 1-yr OS 30%	
		or VNR 30 mg/m ² d1+8 (all q3 wks)	18% (13–23)	OS 28 wks; TTP 19 wks; 1-yr OS 28%	
	Subsequent retrospective analysis ¹³⁵ of PS 2 patients	130	Gem 1000 mg/m ² d1+8 and VNR 25 mg/m ² d1+8	PS 2: 9.1%	OS 36 wks; TTP 18 wks; 1-yr OS 38%
			vs Gem 1200 mg/m ² d1+8	12.2%	Median OS 25 wks; 1-yr OS 23%; TTP 13 weeks
			or VNR 30 mg/m ² d1+8 (all q3 wks)	13.3%	Median OS 18 wks; 1-yr OS 18%; TTP 10 weeks
SICOG ⁹² (Frasci)	120	Gem 1200 mg/m ² d1+8 and VNR 30 mg/m ² d1+8	22% (12–34)	MST: 29 wks vs 18 wks (<i>P</i> <.01) 1-yr OS: 30% vs 13% (<i>P</i> <.01)	
		vs VNR 30 mg/m ² d1+8 (all q3 wks)	15% (7–27)		
Comella ⁹⁴	264 (>70)	Gem 1000 mg/m ² + Pac 80 mg/m ² (both d1+8 q3 wk) vs	32%	Median OS 9.2 months	
		Gem 1000 mg/m ² + VNR 25 mg/m ² (both d1+8 q3 wk) vs	23%	Median OS 9.7 months	
		Pac 100 mg/m ² d1+8+15 q4 wk or	13%	Median OS 6.4 months	
		Gem 1200 mg/m ² d1+8+15 q4 wk	18%	Median OS 5.1 months	

CI = confidence interval; Gem = gemcitabine; HR = hazard ratio; MILES = Multicenter Italian Lung Cancer in the Elderly Study; MST = median survival time; NSCLC = non-small cell lung cancer; NR = not reported; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; RR = response rate; SICOG = Southern Italy Cooperative Oncology Group; TTP = time to progression; VNR = vinorelbine.

are comparable to those observed for chemotherapy in this setting. Furthermore, there is a recently appreciated value to stability of disease, which can provide a significant survival advantage in the absence of dramatic response rates. Anti-EGFR TKIs have also proven safe and tolerable, with acceptable rates of rash and diarrhea, and avoidance of traditional cytotoxic side effects to which the elderly might be particularly predisposed (eg, emesis, cytopenias, neuropathy, etc.).

However, addition of anti-EGFR TKIs to standard chemotherapy has not improved outcomes in elderly patients, consistent with findings from trials^{109,110} in younger patients. While Scagliotti and coauthors¹⁰⁷ demonstrated reasonable tolerability of GEM/gefitinib in

elderly patients, VNR/gefitinib produced truly unacceptable toxicity (in 25 patients, 72% had serious neutropenia, 12% serious diarrhea; 3 treatment-related deaths were observed); moreover, neither arm demonstrated significant improvement in efficacy compared to historical controls. Similarly, Stinchcombe and colleagues¹⁰⁶ demonstrated activity, but more than 10% of patients had serious toxicity of various types, perhaps suggesting more risk than benefit for this combination in this patient population.

Vascular endothelial growth factor (VEGF) is strongly associated with angiogenesis, which in turn is a key element of neoplastic activities; similar to EGFR, overexpression of VEGF has been correlated with poor prognosis in NSCLC.^{111,112} The first commercially available agent

Table 9. Phase II Trials of Single-agent Anti-EGFR TKIs in Elderly NSCLC Patients (>70 years old)

First Author	Line of Treatment	Number of Patients	Drug/Dosing Regimen	RR (SD)	Survival
Copin ¹⁰²	First Second	20 32	Gefitinib 250 mg daily	3% (26%)	NR
Gridelli ¹⁰³	Second	18	Gefitinib 250 mg BID on day 1 and then daily	0% (11%)	MST 4.4 months
Cappuzzo ¹⁰⁴	Second	40	Gefitinib 250 mg daily	5% (45%)	MST 5 months
Johnson ^{*105,146}	First	88	Erlotinib 150 mg daily	10% (41%)	MST 10.9 months

* Prospective study.

BID = twice per day; EGFR = epidermal growth factor receptor; MST = median survival time; NR = not reported; NSCLC = non-small cell lung cancer; RR = response rate; SD = stable disease; TKI = tyrosine kinase inhibitor.

Table 10. Prospective Phase II Trials of Anti-EGFR TKIs Combined With Standard Single-agent Chemotherapy in Elderly NSCLC Patients (>70 years old)

First Author	Line of Treatment	Number of Patients	Drug/Dosing Regimen	RR (SD)	Survival
Stinchcombe ¹⁰⁶	NR	20	Gefitinib 250 mg daily + Doce 30–36 mg/m ² weekly until PD/intolerance	29% (17%)	NR
Scagliotti ¹⁰⁷ (randomized)	First	35	Gefitinib 250 mg daily + Gem 1200 mg/m ² d1+8 (q3 wks)	5.7% (40%)	MST 9.1 months
	First	25	vs Gefitinib 250 mg/d + VNR 30 mg/m ² d1+8 (q3 wks)	0% (44%)	MST 12 months

Doce = docetaxel; EGFR = epidermal growth factor receptor; Gem = gemcitabine; MST = median survival time; NSCLC = non-small cell lung cancer; RR = response rate; SD = stable disease; TKI = tyrosine kinase inhibitor; VNR = vinorelbine.

demonstrated to provide NSCLC patients clinical benefit was bevacizumab (BEV; Avastin, Genentech), an intravenous monoclonal antibody. A randomized phase II trial¹¹³ (proportion of elderly patients not reported) compared CBP/PAC to the same with BEV in two different doses. Higher rates of response and survival, and longer time to progression, were observed in the higher-dose BEV arm, leading to a subsequent phase III study, ECOG 4599.¹¹⁴ Given the significant rate of pulmonary hemorrhage in squamous tumors in the phase II trial, patients with squamous histology were excluded from the phase III trial, as were patients with brain metastases, clotting diatheses or hemoptysis. ECOG 4599 demonstrated that first-line CBP/PAC/BEV provides a significant survival advantage over CBP/PAC alone, with generally manageable toxicity. Of note, 44% of enrolled patients were at least 65 years old; furthermore, subsequent unplanned subset

analysis found that the survival advantage persisted across multiple demographic groups, including age. A formal analysis of outcome in the elderly enrolled to this phase III trial is ongoing.

Other promising anti-VEGF/antiangiogenic agents in various stages of development evaluated for NSCLC include sorafenib¹¹⁵ (Nexavar, Bayer), sunitinib¹¹⁶ (Sutent, Pfizer), and ZD6474¹¹⁷ (Zactima, Wyeth). None of the presented retrospective or prospective data, however, have specifically addressed the safety or efficacy of these agents in the elderly population. Other targeted approaches in NSCLC include the inhibition of proteasome function (with bortezomib^{118,119} [Velcade, Millennium]), cyclooxygenase-II (with celecoxib, [Celebrex, Pfizer]),¹²⁰ or the mammalian target of rapamycin (with RAD001¹²¹), but there are not yet sufficient data specific to the elderly.

Chemotherapy Treatment of NSCLC In Poor-PS Patients

PS has evolved as perhaps the most useful clinical prognostic marker in oncology practice. The two most commonly-used scales are that of the ECOG¹²² and the Karnofsky (KPS);¹²³ studies have demonstrated close approximation between the two scales in most cases.¹²⁴ Compared to patients with good PS (ECOG 0–1, KPS >60%), patients with poor performance status (ECOG 2, KPS <60%) have shorter survival, and are more likely to develop toxicity.^{125,126} However, a seminal meta-analysis¹² found a significant survival benefit from chemotherapy in the PS 2 population, with no clear decrement in the degree of benefit. Until recently, data to determine optimal treatment had been extracted from retrospective analyses.

For example (Table 5), retrospective evaluation¹²⁷ of ECOG 1594 demonstrated similar rates of various toxicities between PS 2 patients and PS 0/1 patients; however, the PS 2 population experienced significantly poorer survival. There were no significant differences in efficacy between the four treatment regimens in PS 2 patients; but median survival was only 4.1 months and the 1-year survival rate was 19%. In the phase III CALGB 9730 trial,⁶³ planned subset analysis of PS 2 patients revealed superior ORR (24% vs 10%), MST (4.7 vs 2.4 months; $P=.016$), and 1-year OS (18% vs 10%) for CBP/PAC, compared to PAC alone. Additionally, QoL analysis suggested no significant negative impact from doublet therapy. Unplanned subset analysis¹²⁸ of the 130 PS 2 patients in the phase III MILES trial (Table 8) demonstrated poorer efficacy but relatively similar rates of serious toxicity compared to the better-PS patients, as well as worse outcome with combination therapy than either single agent (similar to the better-PS group). In multivariate analysis of the phase III study by Comella and associates⁹⁴ (Table 8), PS 0–1 patients were more likely to survive than PS 2 patients (hazard ratio 0.67; 95% confidence interval 0.51–0.90), who constituted 29% of the well-balanced study population. An earlier trial⁹³ of PAC versus best supportive care in 157 NSCLC patients (27 of whom were PS 2) confirmed a survival advantage with chemotherapy; furthermore, the benefit persisted across all PS subgroups.

Prospective phase II trials, some of which also included the elderly, have evaluated systemic therapy in poor-PS NSCLC patients (Tables 2, 4, 7, and 11). Baka and colleagues¹²⁹ evaluated two slightly different schedules of GEM in PS 2 patients, and demonstrated largely equivalent efficacy and safety between arms, except for a nonsignificant trend in QoL and KPS improvement, favoring a monthly schedule. However, there was a significant improvement in the KPS of surviving patients remaining on treatment beyond two cycles for both

groups. A Hellenic Cooperative Oncology Group effort¹³⁰ demonstrated higher rates of response, survival, and time to progression in the doublet arm of GEM/CBP, compared to GEM alone, but these differences were not statistically significant; however, both arms were equivalent (~66% of patients in each arm) in patient-reported improvement in overall status with therapy. Toxicity was generally comparable, albeit with slightly more hematologic toxicity in the combination arm. Given the favorable toxicity data in ECOG 1594, the ECOG conducted a distinct prospective, randomized phase II trial (ECOG 1599) specific to PS 2 NSCLC patients, evaluating both CBP/PAC and CDDP/GEM.^{131,145} Overall response rate and survival endpoints were similar between arms. Neutropenia was the most frequently encountered serious toxicity from CBP/PAC (59% vs 34%), whereas CDDP/GEM was more likely to cause emesis, thrombocytopenia, and mild renal insufficiency. Taken in total, grade 4/5 toxicities were more frequent in the CBP/PAC arm (39% vs 26%). Kaneda and associates¹³² also demonstrated both feasibility and efficacy for chemotherapy in this patient population, noting a slight preponderance of gastrointestinal distress and neuropathy in the CBP/PAC arm in that randomized phase II study, and more hematologic, pulmonary, and hepatic toxicity from GEM/VNR.

The first prospective, randomized, phase III study¹³⁴ conducted in exclusively PS 2 NSCLC patients was presented recently; this effort featured a novel taxane formulation, linking PAC to poly-L-glutamic acid (PAC poliglumex or PPX). Relative to PAC, preclinical work had demonstrated higher stability of PPX in plasma, higher accumulation in tumors, and less need for solubilizing agents (ie, Cremophor). Phase II studies^{135,136} demonstrated efficacy, with a median survival of 8.1 months in PS 0–1 patients, and 5.4 months in PS 2 patients; the drug was also well-tolerated. The feasibility of combination with CBP had also been demonstrated.¹³⁷ STELLAR-3, a phase III randomized trial,¹³⁴ randomized 400 PS 2 patients to either CBP/PAC or CBP/PPX. Treatment with PPX (compared to PAC) was less likely to cause musculoskeletal side effects and alopecia, and also delayed time to neuropathy. However, PPX yielded slightly more GI distress (none grade 3–4) and grade 3–4 thrombocytopenia, and overall neuropathy incidence was similar (~50%). Efficacy endpoints were better than previously reported in retrospective analyses of prior phase III trials.^{63,127}

A similar prospective randomized phase III trial (STELLAR-4) randomized 378 PS 2 NSCLC patients to either receive GEM or VNR (control arm) versus single-agent PPX.¹³⁸ There was no significant difference in outcome with respect to median, 1-, and 2-year survival rates. However, in an unplanned retrospective analysis, the PPX arm appeared superior to VNR when those receiving this agent were isolated.

Table 11. Prospective Phase II Trials of First-line Chemotherapy in NSCLC Patients With Poor PS (ECOG 2, KPS <70%)

First Author/Group	Number of PS 2 Patients	Drug/Dose	RR (SD)	Survival
Baka ¹²⁹ (randomized)	87 87	Gem 1000 mg/m ² d1+8+15 (q4 wks) vs Gem 1500 mg/m ² d1+8 (q3 wks)	7.6% (16%) 7.6% (16%)	MST 83d 1-yr OS 9% MST 65 d (<i>P</i> =.81) 1-yr OS 13%
Kosmidis (HCOG) ¹³⁰ (randomized)	51 51	Gem 1,250 mg/m ² d1+15 (q4 wks) vs Gem 1,250 mg/m ² + Cbp AUC 3 (both d1+15 q4 wks)	4% (21%) 14% (21%)	MST 4.8 mos TTP 2.98 mos 1-yr OS 17.8% MST 6.7 mos (<i>P</i> =.49) TTP 4.07 mos (<i>P</i> =.36) 1-yr OS 20% (<i>P</i> =.8)
Spiridonidis ¹³³	30	Doce 60 mg/m ² d1 + Gem 800 mg/m ² d1+8+15 (both q4 wks)	33%	MST 4.1 mos; 1-yr OS 14%; 2-yr OS 7%
Stinchcombe* ¹⁴⁴ (LCCC 9719/2003)	73 (of 314)	Cbp AUC 6 q3 wks + Pac 75 mg/m ² weekly or Pac 200–225 mg/m ² q3 wks (followed by Pac 80 mg/m ² /wk until PD in LCCC 9719)	26% vs 28%	MST 4.9 mos 1-yr OS 21% vs MST 8.4 mos (<i>P</i> =.0004) 1-yr OS 31%
Tester (ECOG 1599) ^{131,145} (randomized)	103	Cbp AUC 6 + Pac 200mg/m ² (q3 wks) vs CDDP 60 mg/m ² + Gem 1,000 mg/m ² d1+8 (q3 wks)	16% (47%) 25% (35%)	MST 6.1 mos 1-yr OS 19% PFS 3.7 mos TTP 4.2 mos MST 6.8 mos 1-yr OS 25% PFS 3.5 mos TTP 4.8 mos
Kaneda (WJTOG-0004) ¹³² (randomized)	89	Cbp AUC 6 + Pac 200 mg/m ² (q3 wks) vs Gem 1,000 mg/m ² + VNR 25 mg/m ² (both d1+8 q3 wks)	29.3% 20.9%	NR

*Retrospective data.

AUC = area under the curve; Cbp = carboplatin; CDDP = cisplatin; Doce = docetaxel; ECOG = Eastern Cooperative Oncology Group; Gem = gemcitabine; HCOG = Hellenic Cooperative Oncology Group; KPS = Karnofsky performance status; MST = median survival time; NSCLC = non-small cell lung cancer; NR = not reported; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; PS = performance status; RR = response rate; SD = stable disease; TTP = time to progression; VNR = vinorelbine; WJTOG = West Japan Thoracic Oncology Group.

Subsequent analysis¹³⁹ of both PS 2–specific STELLAR trials found weight loss, extrathoracic metastasis, low Lung Cancer Subscale scores, and high lactate dehydrogenase to significantly predict (*P*<.001) a poorer survival. There were also significant differences in efficacy by geographic location, suggesting that regional stratification would be extremely important in future randomized trials. Interestingly, compared to men (OS PPX 7.3

vs control 6.9 months; *P*=.53), treatment with PPX (vs other drugs in these trials) allowed women to achieve superior overall survival (9.5 vs 7.8 months; *P*=.03).¹⁴⁰ Moreover, women under 55 years old (10.0 vs 5.2 months; *P*=.038) were more likely to benefit from PPX over control drug than women over 55 years old (8.9 vs 8.6 months; *P*=.134); similarly, women with higher estrogen levels (>30 pg/dL) obtained more benefit from

Table 12. Prospective Phase III Trials of First-line Chemotherapy in NSCLC Patients With Poor PS

First Author/Group	Number of PS 2 Patients	Drug/Dose	RR (SD)	Survival (Months)
Anderson* ¹⁴¹	213 (of 300)	BSC + Gem 1000 mg/m ² d1+8+15 (q4 wks) vs BSC	19% (NR) NR (NR)	MST 5.7 1-yr OS 25% MST 5.9 (<i>P</i> =.84) 1-yr OS 22%
Langer (STELLAR-3) ¹³⁴	400	Cbp AUC 6 + Pac 225 mg/m ² (q3 wks) vs Cbp AUC 6 + PPX 210 mg/m ² (q3 wks)	36% (37%) 21% (54%)	MST 5.8 TTP 4.6 1-yr OS 19% MST 7.2 TTP 3.9 1-yr OS 28%
O'Brien (STELLAR-4) ¹³⁸	378	PPX 175 mg/m ² (q3 wks) vs Gem 1000 mg/m ² d1+8+15 (q4 wks) or VNR 30 mg/m ² d1+8+15 (q3 wks)	NR NR NR	MST 7.3 1-yr OS 26% 2-yr OS 15% MST 6.6 1-yr OS 28% 2-yr OS 12% MST 6.0 (<i>P</i> =.012, HR 0.60 vs PPX) 1-yr OS 7% 2-yr OS 0%

* Also included a minority of better-PS patients.

AUC = area under the curve; BSC = best supportive care; Cbp = carboplatin; Gem = gemcitabine; HR = hazard ratio; MST = median survival time; NSCLC = non-small cell lung cancer; NR = not reported; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; PPX = paclitaxel poliglumex; PS = performance status; RR = response rate; STELLAR = Selective Targeting for Efficacy in Lung Cancer, Lower Adverse Reactions; TTP = time to progression; VNR = vinorelbine.

PPX than control drugs (10.2 vs 5.5 months; *P*=.039). These data have led to the initiation of a PS 2-specific randomized phase III trial (PIONEER), comparing PAC to PPX in women.

Ongoing trials of chemotherapy in PS-2 patients include that of Santo and colleagues, a phase III study of GEM/vindesine, compared to GEM alone.⁹⁶ As of last publication, 79 elderly good-PS patients had accrued, as well as 28 younger patients with PS 2. Mainwaring and colleagues accrued 64 PS 2 patients at last report in a study comparing weekly DOCE to weekly DOCE/GEM.⁹⁵

Targeted Therapy for NSCLC in PS 2 Patients

Targeted therapies, especially those inhibiting the function of the EGFR or VEGF, have generally not been aggressively evaluated in PS 2 patients; in fact, most trials

have specifically excluded such patients. For example, in pivotal trials of bevacizumab, PS 2 patients were generally under-represented or excluded (only 7% in the randomized phase II trial¹¹³ of BEV/CBP/PAC, and 0% in the phase III E4599).¹¹⁴ However, retrospective evaluation¹⁴² of the gefitinib compassionate access program has yielded some evidence of efficacy and safety, even in heavily-treated patients with significantly impaired PS. In the BR.21 study⁵⁶ of erlotinib compared to best supportive care (BSC), approximately one-third of enrolled patients were PS 2–3, and were evenly distributed between arms. A significantly improved response rate and a prolonged survival time were noted in the treatment arm; this effect was preserved in the PS 2–3 population, although the survival benefit was less significant than in PS 0–1 patients. Lilenbaum and colleagues¹⁴³ conducted a prospective randomized phase II study of erlotinib or standard CBP/

Table 13. Prospective Phase II Trials of Targeted Therapy in NSCLC Patients With Poor PS

First Author	Number of PS 2 Patients	Line of Treatment	Drug/Dose	RR (SD)	Survival
Zinner* ¹⁴²	84 (of 117; also 13 PS 3 and 20 PS 4)	Second and beyond	Gefitinib 250 mg daily	3.3% (38.3%)	Median OS 2 mos 1-yr OS 15.7%
Lilenbaum ¹⁴³ (randomized)	88 (of 102 planned)	First	Erlotinib 150 mg/d vs Cbp AUC 6 + Pac 200 mg/m ² (q3 wks)	2% (30%) 10% (45%)	Median PFS 2.5 mos Median PFS 4 mos
Chaplen ¹²⁰	21 (of 39 planned)	First	Doce 36 mg/m ² d1+8+15 (q4 wks) + CEL 400 mg BID	21% (26%)	MST 5.6 mos TTP 3 mos

* Retrospective data of compassionate access program.

AUC = area under the curve; Cbp = carboplatin; CEL = celecoxib; Doce = docetaxel; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; MST = median survival time; NSCLC = nonsmall cell lung cancer; NR = not reported; OS = overall survival; Pac = paclitaxel; PFS = progression-free survival; PS = performance status; RR = response rate; SD = stable disease; TTP = time to progression.

PAC chemotherapy in this patient population, and demonstrated generally better efficacy in the chemotherapy arm, albeit in preliminary reports. The addition of a cyclooxygenase-II inhibitor to standard weekly docetaxel also proved reasonably efficacious, although due to substantial vascular toxicity, longer follow-up and careful evaluation are required to fully evaluate safety.¹²⁰

Summary

Given the sheer number of advanced NSCLC patients with either advanced age or impaired PS in clinical practice, and their overall poor prognosis, the optimal treatment for such patients must be defined by prospective, randomized, phase III trials. Unfortunately, there has been a relative dearth of such data, until recently. With the advent of less-toxic, rationally-designed targeted therapies, better supportive care, alternative formulations of older chemotherapeutic agents, and cooperative-group attention to these underserved populations, outcomes are expected to improve, and optimal treatment for elderly and PS 2 NSCLC patients will be better defined. As with any significant oncologic intervention, patient selection is absolutely critical, and identification of predictive and prognostic clinicopathologic biomarkers will undoubtedly assist in choosing the optimal therapy for a given patient.

Based on the above data, recommendations currently include careful pretreatment assessment, first-line combi-

nation chemotherapy (platinum- or nonplatinum-based doublet) for selected NSCLC patients, and single-agent chemotherapy for the remainder (and likely the majority) of elderly and/or PS 2 patients. Single-agent chemotherapeutic agents should be third-generation; these include VNR, GEM, DOCE, PAC, and pemetrexed. Whether PPX or any other new cytotoxic agents result in superior outcome compared to PAC remains to be determined.

Targeted therapies with an established role in younger and/or better-PS patients, such as erlotinib or BEV, need to be better investigated in these challenging populations. Erlotinib has clearly shown a survival advantage compared to BSC in the second- and third-line setting that extends to PS 2–3 patients. Bevacizumab, however, needs to be investigated further. With proper risk-benefit discussion, their role in individual patients needs to be considered. Future areas of research include the investigation of new targeted approaches and identification of new targeted therapies, better methods to identify which particular PS 2 patients might benefit from aggressive therapy (ie, which patients have a PS 2 due to cancer, and not comorbidity), and the feasibility of combination treatment with both targeted and chemotherapeutic approaches.

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