

# Optimizing Chemotherapy for Patients with Advanced Non-small Cell Lung Cancer

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**Abstract:** Platinum-based therapy remains the standard of care for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). When combined with a third-generation agent, platinum-based doublets improve survival compared with the third-generation agent given alone. Controversy remains, however, regarding the relative risks and benefits of the third-generation agents. Four large phase III trials have addressed this question, with only one trial finding a survival benefit in one of the treatment arms. TAX 326 compared docetaxel-based therapy with vinorelbine/cisplatin, and found that survival, response, and quality of life outcomes all favoured the docetaxel/cisplatin regimen. Consistent benefits have been reported with this regimen in other studies. The non-platinum-based docetaxel/gemcitabine combination is an alternative for patients who are not suitable candidates for platinum-based therapy. Other results have shown that single-agent docetaxel is an appropriate option for elderly patients and those with poor performance status. Overall, the wealth of data with docetaxel in advanced NSCLC suggests that it plays an important role in first-line treatment and, as a single agent, can be considered a reasonable approach in elderly and frail patients.

**Key Words:** Non-small cell lung cancer, Advanced disease, First-line, Docetaxel, Vinorelbine, Cisplatin.

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## INTRODUCTION

Chemotherapy improves survival for patients with advanced non-small cell lung cancer (NSCLC), and first-line treatment for patients with a good performance status (PS) generally includes two chemotherapy agents with different mechanisms of action and safety profiles. Platinum-based therapy has been the standard for over two decades, and when combined with a third-generation agent such as a taxane, gemcitabine, or vinorelbine, there appears to be a small but significant survival advantage associated with the use of cisplatin over carboplatin (Figure 1).<sup>1</sup> This finding has been confirmed in a second

meta-analysis, which was conducted with individual patient data, and found an 11% reduction in the relative risk of death with cisplatin in this setting ( $p = 0.026$ ).<sup>2</sup> Treatment guidelines now recognize that non-platinum-based doublets can also play a role in the management of advanced NSCLC for selected patients, as can single-agent therapy for elderly patients or those with poor PS.<sup>3</sup> The question remains, however, as to whether there is a preferred third-generation agent to use for the treatment of advanced NSCLC. Accumulating evidence suggests that docetaxel is an effective agent with an acceptable safety profile in the advanced NSCLC population.

## FIRST-LINE THERAPY

The question of which third-generation agent to combine with platinum therapy has been addressed in a number of randomized phase III clinical trials. Most have found no significant differences among the combinations in terms of efficacy (Table 1),<sup>4–7</sup> whereas toxicity profiles, the cost of treatment and quality of life endpoints sometimes varied significantly from one regimen to the others. In the TAX 326 randomized trial comparing standard vinorelbine/cisplatin (VC) with docetaxel/cisplatin (DC) and docetaxel/carboplatin (DCb), treatment with DC produced an 11% increase in survival compared with VC (hazard ratio [HR] 1.183;  $p = 0.044$ ).<sup>7</sup> The median survival time (MST) of 11.3 months with DC is one of the longest demonstrated in recent clinical trials (Table 1); unlike the other three trials, however, a higher proportion of patients with stage III disease were included. In addition, the response rate was significantly higher in the DC arm (32 versus 25%, respectively;  $p = 0.029$ ). The 2-year survival rate was 50% higher with DC (21 versus 14%, respectively;  $p = \text{NS}$ ). Grade 3/4 adverse events were more common in the VC arm (48%) than in either of the docetaxel arms (DC 41%; DCb 40%). There were no differences among treatment groups in the incidence of grade 3/4 neutropenia, thrombocytopenia, or infection. Febrile neutropenia occurred in fewer than 5% of patients in each group. Grade 3/4 anaemia was more common with VC (24 versus 7% with DC and 11% with DCb;  $p < 0.01$  for each comparison). For non-haematological toxicities, grade 3/4 nausea and vomiting were more common with VC than with DC or DCb ( $p < 0.01$  for each comparison). In that study, quality of life (QoL) was prospectively evaluated with the validated Lung Cancer Symptom Scale, and both docetaxel regimens were associated with improvements in

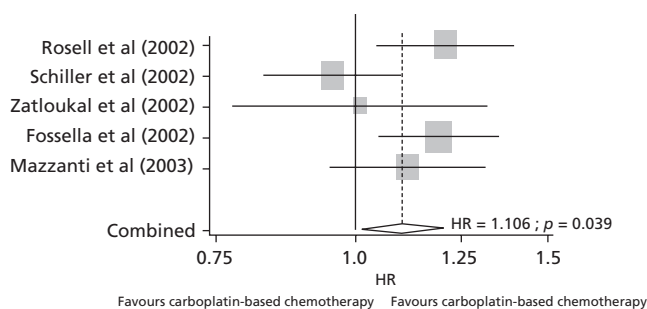
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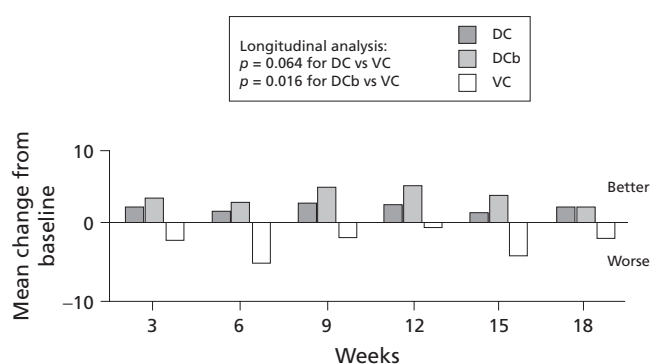


**FIGURE 1.** Overall Survival: Cisplatin Plus New Agent Versus Carboplatin Plus New Agent.<sup>1</sup>

HR, hazard ratio.

QoL, whereas QoL worsened for those receiving VC (Figure 2).<sup>8</sup> Patients treated with DC experienced greater pain relief than did those receiving VC ( $p = 0.033$ ), less deterioration in the PS score ( $p < 0.001$ ), and less weight loss ( $p < 0.001$ ). Overall, the results of the study show that the docetaxel/cisplatin combination improves survival, QoL, and symptom control with an acceptable safety profile in patients with advanced NSCLC.

The survival findings from the TAX 326 study are consistent with the results of other trials of first-line docetaxel/cisplatin (Figure 3).<sup>9,10</sup> Douillard and colleagues<sup>9</sup> conducted a randomized phase II trial of DC compared with VC as first-line therapy in 233 patients with stage IV NSCLC. After six cycles, patients received maintenance therapy with single-agent docetaxel or vinorelbine, respectively, and at progression, patients were crossed over to the other agent as monotherapy. Outcomes were similar for the two treatment arms. The median survival time was 8.3 months with DC and 9.0 months with VC ( $p = 0.38$ ). The 1- and 2-year survival rates were 37 and 17% with DC, and 36 and 10% with VC. In a larger phase III trial, the combination of docetaxel/cisplatin significantly improved MST compared with vindesine/cisplatin in 302 patients with stage IV NSCLC (MST 11.3



**FIGURE 2.** Changes from Baseline in Lung Cancer Symptom Scale Item 'QoL Today' in TAX 326.<sup>8</sup>

DC, docetaxel/cisplatin; DCb, docetaxel/carboplatin; VC, vinorelbine/cisplatin.

months versus 9.6 months, respectively;  $p = 0.014$ ).<sup>10</sup> The 1- and 2-year survival rates were 48 and 24% with DC and 41 and 12% with vindesine/cisplatin.

For patients intolerant of or with a contraindication to platinum-based therapy, a combination of docetaxel/gemcitabine (DG) is a reasonable alternative for first-line therapy. Two phase III clinical trials have demonstrated that this combination is at least as effective as the VC combination but better tolerated.<sup>11,12</sup> In the trial by Pujol et al.<sup>12</sup> ( $N = 311$ ), MST was higher with DG than with VS (11.1 versus 9.6 months), but this difference was not statistically significant. The DG regimen was generally better tolerated than the VC regimen. For example, neither group received prophylactic granulocyte colony-stimulating factor, but the rates of both grade 3/4 neutropenia and febrile neutropenia were significantly lower with DG (52 and 8.4%, respectively) than with VC (83 and 22%, respectively;  $p < 0.001$  for each comparison). Grade 3/4 anaemia was also more common with VC (21 versus 6%;  $p < 0.001$ ). In the trial by Georgoulis et al.<sup>11</sup> ( $N = 413$ ), there were no differences in survival outcomes (MST 9.0 months for DG

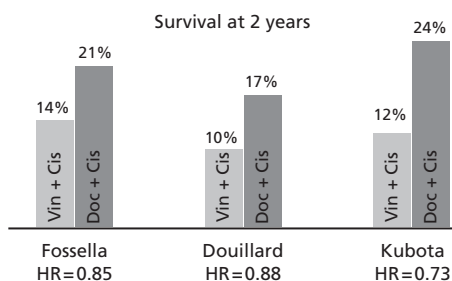
**TABLE 1.** Comparison of Major Randomized Trials in Advanced Non-small Cell Lung Cancer.

	Regimen	N	Stage IV, %	ORR, %	MST, months	1-year OS, %
SWOG 9509 <sup>4</sup>	VC	202	89	28	8.1	36
	Pac225/Cb	206	88	25	8.6	38
ECOG 1594 <sup>5</sup>	Pac135/Cis	288	89	21	7.8	31
	GC	288	86	22	8.1	36
	DC	289	86	17	7.4	31
	Pac225/Cb	290	86	17	8.1	34
ILCP <sup>6</sup>	VC	201	81	30	9.5	37
	GC	205	81	30	9.8	37
	Pac225/Cb	201	82	32	9.9	43
TAX 326 <sup>7</sup>	VC	404	67	25	10.1	41
	DC	408	67	32*	11.3 <sup>†</sup>	46
	DCb	406	67	24	9.4	38

DC, docetaxel/cisplatin; DCb, docetaxel/carboplatin; GC, gemcitabine/cisplatin; MST, median survival time; ORR, overall response rate; OS, overall survival; Pac135/Cis, paclitaxel 135 mg/m<sup>2</sup> plus cisplatin; Pac225/Cb, paclitaxel 225 mg/m<sup>2</sup> plus carboplatin; VC, vinorelbine/cisplatin.

\*  $p = 0.029$  for DC versus VC.

<sup>†</sup>  $p = 0.044$  for DC versus VC.



**FIGURE 3.** Survival at 2 Years in Randomized Trials of First-line Docetaxel/Cisplatin for Advanced Non-small Cell Lung Cancer.<sup>7,9,10</sup>

Cis, cisplatin; Doc, docetaxel; HR, hazard ratio; Vin, vinorelbine.

and 9.7 months for VC) or overall response rates (30 and 39%, respectively). Again, the DG regimen was generally better tolerated than VC. Both groups received prophylactic granulocyte colony-stimulating factor, but the incidence of grade 3/4 neutropenia was significantly reduced with DG (16 versus 37%, respectively;  $p=0.0001$ ), as was the incidence of febrile neutropenia (6 versus 11%;  $p=0.009$ ). Grade 3/4 nausea and vomiting was also more common with VC (15 versus 1%;  $p=0.003$ ). In addition, QoL scores on the Lung Cancer Symptom Scale were improved from baseline in the DG group for haemoptysis and pain; no changes in symptom scores were seen in the VC group from baseline to end of therapy.

### Meta-Analysis

When summarizing the results of all of the published comparative clinical trials of docetaxel-based compared with vinca alkaloid-based therapy, it becomes clear that the point estimates for overall survival in each trial tend to favour docetaxel. Meta-analysis is a useful tool to define more precisely the magnitude of treatment benefit associated with therapy. Douillard and colleagues<sup>13</sup>

recently conducted a meta-analysis to estimate more precisely the magnitude of benefit of docetaxel-based therapy in advanced NSCLC. The analysis included all trials that compared docetaxel-based with vinca alkaloid-based therapy in this setting, without restriction by language. Doublet and single-agent therapy trials were included, as were published papers (Table 2)<sup>7,9-12,14</sup> and meeting abstracts. All investigators were contacted in an effort to obtain the most accurate and updated results of the studies considered. Overall survival was the primary endpoint of the analysis. Serious adverse events and haematologic toxicity were also assessed. Sensitivity analyses included a comparison of docetaxel and vinorelbine trials, doublet trials only, and analysis with deletion of each trial one by one.

Once the data were reviewed, they were presented at the 2006 annual meeting of the American Society of Clinical Oncology (ASCO). Overall, this meta-analysis provides the first evidence that one third-generation agent, docetaxel, is superior to another, vinorelbine, in the first-line treatment of patients with advanced NSCLC. Further results will be forthcoming soon.

### SPECIAL POPULATIONS

Lung cancer is frequently diagnosed in the elderly. Even though the majority of diagnoses are made in patients over the age of 65 years, they comprise only 39% of patients in clinical trials, and patients over the age of 80 years are often excluded from trials by virtue of age alone.<sup>15</sup> Therefore, few data are available to guide treatment decisions for older patients, particularly those with multiple co-morbidities or poor PS. Current clinical practice guidelines from the ASCO recommend single-agent chemotherapy for elderly patients with advanced NSCLC.<sup>3</sup> The value of non-platinum-based, single-agent therapy has been demonstrated in several trials conducted in patients 70 years of age or older. The Elderly Lung Cancer Vinorelbine

**TABLE 2.** Published Trials of Docetaxel Versus Vinca Alkaloids in First-Line Advanced Non-small Cell Lung Cancer.

Trial	Population	Docetaxel Regimen	Vinca Alkaloid Regimen
TAX 326 <sup>7</sup>	IIIB/IV N = 1218	DC D 75 mg/m <sup>2</sup> d1 Q3W C 75 mg/m <sup>2</sup> d1 Q3W DCb D 75 mg/m <sup>2</sup> d1 Q3W Cb AUC6 d1 Q3W	VC V 25 mg/m <sup>2</sup> d1, 8, 15, 22 Q4W C 100 mg/m <sup>2</sup> d1 Q4W
Taxobel 303 <sup>9</sup>	IV N = 233	DC D 75 mg/m <sup>2</sup> d1 Q3W C 100 mg/m <sup>2</sup> d1 Q3W	VC V 30 mg/m <sup>2</sup> d1, 8 Q3W C 100 mg/m <sup>2</sup> d1 Q3W
TAX 301 <sup>10</sup>	IV N = 311	DC D 60 mg/m <sup>2</sup> d1 Q3-4W C 80 mg/m <sup>2</sup> d1 Q3-4W	VdC Vind 3 mg/m <sup>2</sup> d1, 8, 15 Q4W C 80 mg/m <sup>2</sup> d1 Q4W
Georgoulas et al. <sup>11</sup>	Inoperable, IIIB/IV N = 413	DC D 100 mg/m <sup>2</sup> d8 Q3W G 1000 mg/m <sup>2</sup> d1, 8 Q3W	VC V 30 mg/m <sup>2</sup> d1, 8 Q3W C 80 mg/m <sup>2</sup> d1, 8 Q3W
Pujol et al. <sup>12</sup>	IV N = 311	DG D 85 mg/m <sup>2</sup> d8 Q3W G 1000 mg/m <sup>2</sup> d1, 8 Q3W	VC V 30 mg/m <sup>2</sup> d1, 8, 15, 22 Q4W C 100 mg/m <sup>2</sup> d1 Q4W
WJTOG 9904 <sup>14</sup>	Elderly, IIIB/IV N = 180	D D 60 mg/m <sup>2</sup> d1 Q3W	V V 25 mg/m <sup>2</sup> d1, 8 Q4W

C, cisplatin; Cb, carboplatin; d, day; D, docetaxel; DC, docetaxel/cisplatin; DCb, docetaxel/carboplatin; DG, docetaxel/gemcitabine; G, gemcitabine; Q3W, every 3 weeks; Q4W, every 4 weeks; V, vinorelbine; VC, vinorelbine/cisplatin; VdC, vindesine/cisplatin; Vind, vindesine.

Study (ELVIS) Group first demonstrated that single-agent vinorelbine improved survival and QoL over best supportive care in this population in the phase III ELVIS trial.<sup>16</sup> Subsequent randomized trials evaluated single-agent therapy compared with a combination of vinorelbine/gemcitabine, with conflicting results. The Southern Italy Cooperative Group compared vinorelbine with gemcitabine/vinorelbine in 120 patients, and found significant improvements in median survival with combination therapy (MST 29 versus 18 weeks, respectively;  $p < 0.01$ ), as well as a delay in the worsening of symptoms and QoL.<sup>17</sup> Conversely, the Multicenter Italian Lung Cancer in the Elderly Study, which compared vinorelbine, gemcitabine, and the combination of the two in 698 elderly patients, found that the combination was not superior to either single-agent regimen.<sup>18</sup> Median survival times were 36 weeks, 28 weeks, and 20 weeks, respectively ( $p = \text{NS}$ ). Although QoL did not differ among treatment arms, a greater rate of toxicity was seen with combination therapy. Independently of the results of the above-mentioned studies, there is an increasing line of clinical evidence that age alone is not a sufficient factor to exclude patients between 70 and 75 years of age without severe co-morbid conditions from receiving combination chemotherapy.

Given its efficacy in NSCLC, several groups have evaluated docetaxel in elderly patients with advanced disease. The West Japan Thoracic Oncology Group recently published complete results from WJTOG 9904, a phase III trial comparing docetaxel with vinorelbine as first-line therapy in elderly patients with advanced NSCLC.<sup>14</sup> A total of 182 patients with stage IIIB/IV NSCLC with PS 0–2 were enrolled. Response rates and progression-free survival were improved in the docetaxel arm; overall survival was longer in the docetaxel arm, but not statistically significantly different (Table 3). There were no differences in global QoL between the two arms; however, docetaxel was associated with a significant improvement in symptom scores, particularly for measures of anorexia and fatigue. Both treatments were generally well tolerated by elderly patients. Notably, grade 3/4 haematological toxicity was significantly more common with docetaxel (grade 3/4 neutropenia 83 versus 69%, respectively;  $p = 0.031$ ), but the incidence of febrile neutropenia did not differ between arms (13 versus 11%, respectively). That trial demonstrates that docetaxel monotherapy is an appropriate option for elderly patients with advanced NSCLC.

Docetaxel-based doublets have also been evaluated in elderly patients in clinical trials. In a preplanned subgroup analysis of TAX 326, Belani and Fossella<sup>19</sup> found that patients aged 65 years and older receiving DC obtained benefits similar to those of their younger counterparts. For the 401 elderly patients in the study, median survival was 12.6 months with DC compared with 9.9 months with VC. One-year survival was 52 and 41%, respectively, with 2-year survival rates of 24 and 17%, respectively. Rates of grade 3/4 toxicity (in particular asthenia, infection, pain, neurotoxicity, and pulmonary toxicity) were generally greater in the elderly population than in the younger cohort in all three treatment arms. Fewer patients receiving DC (20%) discontinued treatment because of an adverse event compared with those receiving VC (32%).

A weekly combination of docetaxel/cisplatin was safely administered to fit, elderly patients in a small study in Japan, where elderly patients are routinely excluded from trials based on age alone.<sup>20</sup> In that phase II trial, 33 patients aged 75 years and older with PS 0/1 received cisplatin 25 mg/m<sup>2</sup> and docetaxel 20 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle. The weekly dosing strategy was chosen because of concerns related to the toxicity of full-dose cisplatin administered once per cycle to this population. The results of this phase II trial are encouraging, with respect to both response and tolerability. The majority of patients responded to treatment (overall response rate 52%), with a median survival time of 15.8 months. Grade 4 toxicity was not observed, whereas grade 3 neutropenia occurred in 12% of patients. The Japanese Clinical Oncology Group is currently conducting a randomized phase III trial (JCOG0207) comparing weekly single-agent docetaxel with weekly docetaxel plus cisplatin in NSCLC patients 70 years of age and older.<sup>21</sup> Results are expected in 2007, and will provide important information about the risks and benefits of doublet therapy in elderly patients with advanced NSCLC.

Performance status is a well-known independent prognostic factor. Median survival and response rates are both lower for PS 2 patients than for those with PS 0 or PS 1.<sup>22</sup> There is a continued perception that the risk of toxicity is greater for PS 2 patients, and the current ASCO clinical practice guidelines recommend single-agent chemotherapy for both PS 2 and elderly patients.<sup>3</sup> Guidelines from the European Expert Panel, however, recognize that there is a need to distinguish elderly patients from poor PS patients.<sup>22</sup> At the current time,

**TABLE 3.** Results of WJTOG 9904: Docetaxel Versus Vinorelbine in Elderly Patients.<sup>14</sup>

	Docetaxel (n = 88)	Vinorelbine (n = 91)	P value
Median survival, months	14.3	9.9	0.14
Progression-free survival, months	5.5	3.1	< 0.001
Overall response rate, %	23	10	0.019
Complete response, %	0	0	
Partial response, %	23	10	
Stable disease, %	53	50	
Progressive disease, %	21	37	
Not assessable	3	3	

docetaxel-based therapy has been evaluated in the combined population of elderly/poor PS patients.

Weekly docetaxel retains efficacy but has improved tolerability over standard therapy in elderly/poor PS patients with advanced NSCLC.<sup>23</sup> Docetaxel 30 mg/m<sup>2</sup> given on days 1, 8, and 15 every 4 weeks was compared with docetaxel 75 mg/m<sup>2</sup> every 3 weeks as first-line therapy for patients 70 years of age or older (with PS 0–2) or patients of any age with PS 2. The median age was 75 years; approximately half of the patients were PS 2. There were no differences between groups with regard to the overall response rate or median survival time among the 69 evaluable patients. The incidence of grade 3/4 neutropenia was, however, significantly reduced with weekly therapy (no cases with weekly therapy versus 30% with 3-weekly docetaxel;  $p=0.0001$ ).

Although clinical trials generally demonstrate the tolerability of docetaxel in elderly and PS 2 patients, it should be noted that some patients experience side effects, such as facial swelling, leg oedema, and the new development or worsening of pleural effusion, which may be more common with dosing every 3 weeks. Because these events may be cumulative in nature, they can become a limiting factor for some patients in our practices. Another relevant issue, especially for women, is the potential for complete alopecia. Clinicians should discuss the risks and benefits of therapy with each patient.

In conclusion, docetaxel-based doublets are among the most active treatments in advanced NSCLC, with survival and QoL benefits demonstrated for the docetaxel/cisplatin combination in one of the largest phase III trials conducted to date.<sup>7</sup> For patients who are not suitable candidates for platinum-based therapy, a combination of docetaxel/gemcitabine is a viable treatment option, with efficacy similar to that of vinorelbine/cisplatin but improved tolerability. In special populations such as the elderly or patients with PS 2, single-agent docetaxel is an option. Weekly dosing may be appropriate for patients with poor PS. Results from ongoing trials will further define the role of docetaxel-based doublets in poor PS and elderly patients with advanced NSCLC.

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