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Evidence-based Series 7-19 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer

J. Noble, P. Ellis, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group

An assessment conducted in November 2013 put Evidence-base Series EBS 7-19 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
This EBS report is available on the CCO Web site (http://www.cancercare.on.ca), consists of the following four sections:

Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: EBS Development Methods and External Review Process and Results
Section 4: Guideline Review Summary

Release Date: October 5, 2012

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Mar 2006	1996-2005	Full Report	Web publication	N/A
Reviewed Version Oct 2012	2005- 2012	New data found in Section 4: Document Summary and Review Tool		2006 recommendations require an **UPDATE**

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Evidence-based Series 7-19: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer: A Clinical Practice Guideline

J. Noble, P. Ellis, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group

Report Date: March 27, 2006

The 2006 guideline recommendations require an

UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012.

This practice guideline expands on and replaces an earlier practice guideline on single-agent second-line docetaxel as treatment for advanced non-small cell lung cancer. That practice guideline was completed in 2001 and published as: Logan D, Laurie S, Markman BR, McNeil M, Vincent M, Evans WK, and the Lung Cancer Disease Site Group. The role of single-agent docetaxel as second-line treatment for advanced non-small-cell lung cancer. Curr Oncol. 2001;8:50-9.

Guideline Question

1. What are the survival and/or quality of life (QOL) benefits of systemic therapy compared with best supportive care (BSC) in the second-line and subsequent treatment of recurrent or progressive non-small cell lung cancer (NSCLC)?
2. Which systemic therapy agent or combination of agents provide the greatest improvement in survival and/or QOL in the second-line and subsequent treatment of recurrent or progressive disease?
3. What are the optimal doses and schedules of different systemic therapy agents in the second-line or subsequent treatment of recurrent or progressive disease?

Tumour response rate, symptom control, and toxicity were secondary outcomes of interest.

Target Population

These recommendations apply to adult patients with advanced or metastatic NSCLC that has recurred or progressed following prior systemic therapy.

Recommendations and Key Evidence

Single-agent docetaxel (Taxotere®) at a dose of 75 mg/m^2 every three weeks is recommended as second-line therapy for patients with recurrent or progressive NSCLC and adequate performance status (0-2).

There is evidence from two randomized phase III trials of a significant benefit in overall survival and QOL for single-agent docetaxel when used as second-line therapy for recurrent or progressive NSCLC. In one trial, comparing docetaxel at 75 mg/m^2 to BSC, median survival was increased from 4.6 months to 7.5 months (p=0.01 log rank), and one-year survival from 12% to 37% (p=0.003 chi-square). Treatment with docetaxel was also associated with a significant improvement in patient-related pain compared to BSC (p=0.005). In a second trial, comparing docetaxel with vinorelbine or ifosfamide, median survival was not significantly different, but one-year survival was superior for docetaxel at 75 mg/m^2 (32% versus 19%, p=0.025, chi-square). Although the optimal duration of therapy is unknown, in both trials, treatment with docetaxel was continued until disease progression or development of unacceptable toxicity.

Single-agent pemetrexed (Alimta®) at a dose of 500 mg/m^2 every three weeks is also an option for second-line therapy of recurrent or progressive disease, if available. This chemotherapy should be administered with vitamin supplements: oral folic acid 350-1,000 mcg daily and intramuscular vitamin B_{12} 1,000 mcg every nine weeks, beginning between one to two weeks before, and continuing until three weeks after chemotherapy.

The results of a single randomized phase III trial suggest a similar survival benefit for single-agent pemetrexed at 500 mg/m^2, combined with vitamin supplementation, compared to docetaxel at 75 mg/m^2, when used as second-line therapy. Median survival was 8.3 months for pemetrexed versus 7.9 months for docetaxel, with one-year survival of 29.7% for both treatments. A test for non-inferiority using the percent retention method, indicated that pemetrexed retained >50% of the survival benefit of docetaxel over BSC (p=0.047). However, the primary test of non-inferiority, which required that survival for pemetrexed be ≤ 10% worse than docetaxel, was not statistically significant (p=0.226). Hematologic toxicities, including febrile neutropenia, occurred with significantly lower frequency with pemetrexed than with docetaxel. A comparison of QOL measures showed no significant difference between the two treatments.

Oral topotecan at a dose of 2.3 mg/m^2 administered day 1-5 every three weeks is not recommended for second-line therapy of recurrent or progressive disease.

The results of a single randomized phase III trial suggest a similar one-year survival rate for oral topotecan at a dose of 2.3 mg/m^2 compared to docetaxel at 75 mg/m^2, when used as second-line therapy. The one-year survival was 25.1% for topotecan versus 28.7% for docetaxel; however, the overall survival difference approached statistical significance in favour of docetaxel (hazard ratio, 1.16; 95% confidence interval, 1.00-1.35; p=0.057), with a median survival of 27.9 weeks and 30.7 weeks for topotecan and docetaxel, respectively. A comparison of QOL measures also significantly favoured docetaxel.

Docetaxel administered at a dose of 33.3-40 mg/m^2 (for six weeks on an eight-week cycle or for three weeks on a four-week cycle) may be considered in patients at high risk of hematologic toxicity or with a previous history of febrile neutropenia using the three-weekly docetaxel schedule.

Evidence from four randomized trials suggests that docetaxel administered weekly at a dose of between 33.3 mg/m^2 and 40 mg/m^2 may achieve similar survival and superior tolerability to docetaxel administered three-weekly at a dose of 75 mg/m^2. A pooled analysis of six-month survival data from those trials provided a hazard ratio of 0.99 (95% confidence interval, 0.84-1.16, p=0.91). The benefit for the weekly regimen in terms of a reduction in the incidence of febrile neutropenia approached statistical significance (hazard ratio, 0.29; 95% confidence interval, 0.08-1.12, p=0.07). However, this potential advantage must be weighed against the greater inconvenience to the patient of weekly treatment.

Combination chemotherapy (docetaxel-based or other) is not currently recommended as second-line or subsequent therapy for recurrent or progressive disease.

Docetaxel-based and other combination chemotherapy regimens have yet to be compared to single-agent docetaxel in a fully published randomized phase III trial. The results of several small trials suggest promising activity for some combination regimens, but those regimens will require further testing.

Erlotinib at a dose of 150 mg/day is recommended as third-line therapy for patients with advanced recurrent or progressive NSCLC who maintain a good performance status following previous platinum-based and docetaxel (or pemetrexed) chemotherapy. Erlotinib is also an option for second-line therapy, particularly in patients who are not candidates for chemotherapy or for those with progression after first-line docetaxel-platinum chemotherapy.

There is evidence from a single randomized phase III trial of a significant benefit in overall survival and QOL for the epidermal growth factor receptor inhibitor (EGFRI) erlotinib (Tarceva®) when compared to placebo as second or third-line systemic therapy. Median survival was increased from 4.7 months to 6.7 months (p<0.001 log rank), and one-year survival from 22% to 31%. Erlotinib was also associated with a significant delay in time to deterioration for cough (p=0.04), dyspnea (p=0.03) and pain (p=0.04), and an improvement in overall physical QOL (p=0.01), compared to placebo.

Gefitinib at a dose of 250 mg/day may be considered for second-line and subsequent therapy only for selected symptomatic patients who are not candidates for chemotherapy and for whom erlotinib is not available.

The results of a single randomized phase III trial revealed no statistically significant survival or QOL benefit for the EGFRI gefitinib (Iressa®) when compared to placebo as second-line or subsequent therapy. Gefitinib was associated with a superior tumour response rate (8% vs 1%, p<0.0001) and symptom improvement. Two randomized phase II trials suggest that modest tumour response rates and symptom control can be achieved with gefitinib. Although a significant survival benefit has not been demonstrated for this agent in a placebo-controlled study, the trials suggest that gefitinib may provide clinically important symptomatic benefits.

Related Guidelines

- PG#7-9, *Use of the epidermal growth factor receptor inhibitors, gefitinib (Iressa®) and erlotinib (Tarceva®), in the treatment of NSCLC*
- PG#7-10, *The role of first-line systemic chemotherapy in the treatment of advanced NSCLC* (currently under development).

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Evidence-based Series 7-19: Section 2

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Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer: A Systematic Review

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Report Date: March 27, 2006

QUESTIONS

1. What are the survival and/or quality of life (QOL) benefits of systemic therapy compared with best supportive care (BSC) in the second-line and subsequent treatment of recurrent or progressive non-small cell lung cancer (NSCLC)?
2. Which systemic therapy agent or combination of agents provide the greatest improvement in survival and/or QOL in the second-line and subsequent treatment of recurrent or progressive disease?
3. What are the optimal doses and schedules of different systemic therapy agents in the second-line or subsequent treatment of recurrent or progressive disease?

Tumour response rate, symptom control, and toxicity were secondary outcomes of interest.

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths in Canada, with an estimated 22,000 Canadians diagnosed and 19,000 dying of the disease in 2004 (1). Non-small cell lung cancer accounts for approximately 70-80% of all lung cancer diagnoses (2) and most deaths from the disease. The great majority of patient deaths from NSCLC occur in the setting of advanced disease, which is commonly present at initial presentation or at relapse. The five-year survival for stages IIIB and IV NSCLC are typically less than 5% (2).

Standard first-line systemic therapy for advanced NSCLC is platinum-based combination chemotherapy, with a regimen that includes cisplatin or carboplatin together

with one or other of vinorelbine, gemcitabine, paclitaxel, or docetaxel (see the Lung Cancer Disease Site Group [Lung DSG] practice guideline report #7-10, *The Role of First-Line Systemic Chemotherapy in the Treatment of Advanced NSCLC*). The median survival for patients with advanced disease treated with those regimens is in the range of 7.4-11.3 months, with one-year survival rates of approximately 30-45% (3-7). Approximately 30-40% of trial patients relapsing or progressing after first-line therapy go on to receive second line chemotherapy (3-5,7). In 2001, the Lung Cancer Disease Site Group (Lung DSG) recommended single-agent docetaxel at a dose of 75 mg/m^2 every three weeks as second-line treatment for suitable patients with advanced or metastatic NSCLC who progressed following platinum-based combination chemotherapy (8). At that time, the median survival for patients treated with that agent was reported as between 5.7 and 7.9 months.

Over the last few years, a number of potential alternatives to single-agent docetaxel have emerged for second-line and subsequent systemic therapy of NSCLC, including single-agent pemetrexed, single-agent topotecan, docetaxel-based and other combination chemotherapy regimens, and the epidermal growth factor receptor (EGFR) inhibitors gefitinib and erlotinib (see the Lung DSG practice guideline #7-9, *Use of Gefitinib and Erlotinib in the Treatment of NSCLC*). At the same time, efforts have been made to improve the tolerability of single-agent docetaxel, by modifying the dose and schedule of treatment. In light of these developments, the Lung DSG felt that an updated review of the literature was warranted. This systematic review summarizes the evidence for each of those options.

METHODS

This systematic review was developed by the Lung DSG of Cancer Care Ontario's Program in Evidence-based Care. Evidence was selected and reviewed by two members of the DSG. All members of the DSG disclosed potential conflict of interest information.

This systematic review is a convenient and up-to-date source of the best available evidence on the use of second-line or subsequent systemic therapy in the treatment of recurrent or progressive NSCLC. The body of evidence in this systematic review is comprised of data primarily from mature randomized controlled trials; it forms the basis of a clinical practice guideline developed by the Lung DSG. This systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. An earlier systematic review and practice guideline on the use of single-agent docetaxel as second-line treatment for advanced NSCLC was published by the Lung DSG in 2001 (8). The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The electronic databases, MEDLINE (1996 through November Week 3 2005), EMBASE (1996 through 2005, week 53), and the Cochrane Library (2005, Issue 4), were searched using the search terms detailed in Appendix A.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO), the European Cancer Conference (ECCO), the European Society for Medical Oncology (ESMO), and the International Association for the Study of Lung Cancer (IASLC) were searched for abstracts of relevant trials published between 2000 and 2005. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

The initial literature searches were reviewed by one member of the DSG, and articles that did not meet the broad inclusion criteria were excluded (i.e. general review articles,

study type or design was not applicable, trials focusing on disease types other than NSCLC, trials of first-line therapy, and trials not involving systemic therapy). Two reviewers selected relevant articles and abstracts from the remaining literature, resolving any disagreements on article selection by discussion. The reference lists from the selected articles were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Articles published as full reports or as abstracts were selected for inclusion in this systematic review of the evidence if they focused on second-line or subsequent systemic therapy for recurrent or progressive NSCLC, reported outcomes of interest, and were:

1. Systematic reviews or practice guidelines of systemic therapy; or
2. Meta-analyses comparing systemic therapy with BSC or another systemic therapy; or
3. Randomized trials comparing different systemic therapy agents or regimens, or systemic therapy with BSC; or
4. Randomized trials comparing different doses and/or schedules of systemic therapy agents.

The following were excluded from the systematic review of the evidence:

1. Systematic reviews or meta-analyses that pre-dated, or confined their analysis to, trials included in the 2001 practice guideline developed by the Lung DSG on the role of single-agent docetaxel as second-line treatment for advanced NSCLC (8).
2. Trials that included a mix of untreated and previously treated patients.
3. Articles published in a language other than English.
4. Trials that included less than 50 patients per trial arm. Trials with less than 100 patients were considered underpowered to detect any clinically meaningful difference in effect given the range of typical accrual times, follow up times, and times-to-event. Trials with less than 50 patients per trial arm are reported in Appendix B and are included in any relevant meta-analyses conducted.

Synthesizing the Evidence

A pooled analysis of mortality data from randomized trials (phase II and III) of weekly versus three-weekly administration of second-line or subsequent single-agent docetaxel was pre-planned. The meta-analysis was conducted on six-month survival data extrapolated from published survival curves, using the Review Manager software, RevMan 4.2.7, (9) available from the Cochrane Collaboration (www.cochrane.org). To limit the potential for error, two researchers independently extrapolated the six-month data from the survival curves, and the average of the two estimates was used in the analysis. However, data censored on the survival curves was not accounted for, which may limit the reliability of the results (10).

In addition, a post-hoc meta-analysis, also using the Review Manager software, was conducted to explore the impact of a weekly versus three-weekly docetaxel schedule on the incidence of grade 3/4 febrile neutropenia. This analysis was based on the number of patients who reported experiencing an event in each treatment arm compared with the number of patients who were available for toxicity evaluation. Where not provided, the latter number was assumed to equal the number of patients randomized.

Results of the meta-analyses are expressed as a relative risk or risk ratio with 95% confidence intervals (CI), where relative risk<1 indicates a benefit for weekly administration of docetaxel and relative risk>1 suggests a benefit for three-weekly administration. The random-effects model was used for comparative testing of the pooled results across studies in preference to the fixed-effects model, as the more conservative estimate of effect (11). Sensitivity analyses were also conducted to explore the impact of including data from abstract reports.

RESULTS

Literature Search Results

Trials meeting the pre-specified eligibility criteria for this systematic review are summarized in Table 1. Trials that randomized less than 50 patients per arm were considered ineligible (Appendix B). Multiple reports of the same study were included in this practice guideline if each report provided additional relevant data. Data from slide presentations associated with abstract trial reports were also included if the presentations were publicly available on meeting Web sites and they provided additional relevant data. In addition, three recent evidence-based clinical practice guidelines addressing the use of second-line chemotherapy for advanced NSCLC met the eligibility criteria for this systematic review and were included (12-15).

Practice Guidelines

Three evidence-based guidelines, developed by ASCO in 2003 (12), the National Institute for Clinical Excellence in 2005 (13,14) and the Scottish Intercollegiate Guidelines Network (SIGN) (15), made recommendations for the diagnosis or treatment of lung cancer and include a section on the use of second-line chemotherapy for NSCLC. All three guidelines recommend docetaxel monotherapy as second-line treatment for appropriate patients with locally advanced or metastatic NSCLC that has relapsed or progressed after first-line chemotherapy (12-15), based primarily on evidence from two randomized controlled trials (16,17) reported in the earlier Lung DSG guideline (8). The ASCO guideline limited that recommendation to patients with an adequate performance status (PS) who had previously received platinum-based chemotherapy (12). In addition, the ASCO guideline considered the use of targeted agents and recommended gefitinib for locally advanced or metastatic NSCLC that had relapsed or recurred after prior treatment with both platinum-based and docetaxel chemotherapy. The latter recommendation was based on the Iressa Dose Evaluation in Advanced Lung cancer (IDEAL) trials (18,19), which are reviewed in the current guideline report.

Table 1. Studies included in this systematic review.

Comparisons	Number of Fully Published Studies (Abstracts)	Reference Numbers	Further Information Found in Table(s)
Chemotherapy agents			
Single-agent docetaxel compared with BSC or another single agent	3 (1)	(16,17,20-24)	Tables 2a and 2b
Single-agent docetaxel dose/schedule comparisons	4 (1)	(25-30)	Tables 3a and 3b
Docetaxel-based combination chemotherapy comparisons	2 (2)	(31-37)	Tables 4a and 4b
Other combination chemotherapy comparisons	2	(38,39)	Tables 5a and 5b
Other systemic therapy agents			
Single-agent EGFR inhibitor comparisons with BSC or another single agent	2 (1)	(40-43)	Tables 6a and 6b
Single-agent EGFR inhibitor dose/schedule comparisons	2 (0)	(18,19)	
Novel systemic therapy agents	0 (4)	(44-50)	Tables 7a and 7b

Abbreviations: BSC = best supportive care, EGFR = epidermal growth factor receptor.

Clinical Trials

The majority of randomized trials considered in this systematic review enrolled a mixture of patients with regard to the number of lines of systemic therapy previously received. Although most of the trials described the patient sample in these terms, few reported outcomes specifically by line of therapy, with the exception of those trials limiting enrolment to patients receiving a specific number of prior therapies.

Chemotherapy

Single-agent docetaxel compared with BSC or another single agent

Four randomized phase III trials compared single-agent docetaxel with either BSC or another single-agent chemotherapy as second-line or subsequent therapy for relapsed or progressive NSCLC (16,17,20-24). The patient characteristics and key treatment outcomes for the trials are summarized in Tables 2a and 2b. One trial was published in abstract form only and provided limited data on which to assess the trial quality (23,24). All trials were described as randomized, multicentre, industry-supported and were stratified by PS; however, the method of randomization was not described in detail, and none reported blinding of treatment assignment for researchers or patients. Survival was the primary outcome, with survival analyses conducted on an intent-to-treat basis. Each trial also included QOL as an endpoint. One trial did not report the pre-determined required sample size, and the estimated power of the trial was based on a non-inferiority hypothesis that the survival time for the experimental treatment would not be greater than 10% worse than for the reference treatment arm (21).

The TAX 317 randomized phase III trial compared docetaxel with BSC (16). The trial was initially designed to compare docetaxel at a dose of 100 mg/m^2 three-weekly (D100); however, an excess of treatment-related deaths led to a dose reduction to 75 mg/m^2 (D75) for patients enrolled in the second half of the trial. Treatment was continued until disease progression or unacceptable toxicity. Comparison of survival outcomes revealed a significant benefit for treatment for the combined docetaxel arms over BSC, and for D75 versus BSC75, but no difference in survival for D100 versus BSC100.

Table 2a: Trials of single-agent docetaxel compared with BSC or another single agent: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]					
			Treatment Line 2nd/3rd/4th+	Prior Therapy: Platin	Prior Therapy: Taxane [d]	PD with prior CT	Disease Stage III/IV	PS [e] 0-1 / 2
Randomized phase III trials								
Shepherd 2000 (16,20) (TAX 317)	Docetaxel 100	49	67 / 16 / 16	100	0	18	18 / 82	78 / 22
	Docetaxel 75	55	80 / 13 / 7	100	0	18	27 / 73	75 / 25
	Docetaxel 100 & 75 combined	104	74 / 14 / 12	100	0	18	23 / 77	76 / 24
	BSC	100	76 / 15 / 9	100	0	20	19 / 81	75 / 25
Fossella 2000 (17,22) (TAX 320)	Docetaxel 100	125	65 / 35 (3rd+)	100	31	33	14 / 86	83 / 17
	Docetaxel 75	125	74 / 26 (3rd+)	100	42	24	10 / 90	82 / 18
	Vinorelbine / Ifosfamide	89 / 34	71 / 29 (3rd+)	100	41	32	9 / 91	85 / 15
Hanna 2004 (21) (JMEI)	Docetaxel	288	100 / 0 / 0	89.9	27.8	31	25 / 75	88 / 12
	Pemetrexed [f]	283	100 / 0 / 0 [g]	92.6	25.8	27	25 / 75	89 / 11
Ramlau 2005 [h] (23,24) (387)	Docetaxel	415	100 / 0	NR	NR	NR	28 / 72	84 / 16 [i]
	Topotecan	414	100 / 0				26 / 74	86 / 14

Abbreviations: BSC = best supportive care, CNS = central nervous system, CT = chemotherapy, NR = not reported, PD = progressive disease, PS = performance status.

[a] Treatment regimens are described in detail in Appendix C.

[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.

[c] All trials allowed for inclusion of patients with CNS metastases which were stable and/or asymptomatic.

[d] Prior taxane allowed was paclitaxel (17,21).

[e] Based on the Eastern Cooperative Oncology Group scale (16,17,20-24).

[f] Patients given pemetrexed also received vitamin supplementation.

[g] Additional neo-/adjuvant chemotherapy was allowed and was not considered as a prior chemotherapy regimen for advanced disease for patient eligibility but was considered as a prior chemotherapy regimen for stratification.

[h] Abstract

[i] One patient given docetaxel had a PS of 4

Table 2b: Trials of single-agent docetaxel compared with BSC or another single agent: trial outcomes.

Reference	Treatment [a]	Response Rate (CR+PR) [b]	Survival Median, Months (95% CI)	Survival 1-year (95% CI)	Survival Overall	Qualify of Life [c]	Common grade 3 or 4 Toxicity (>5% of Patients)
Randomized phase III trials							
Shepherd 2000 (16,20) (TAX 317)	Docetaxel 100 Docetaxel 75 Docetaxel 100 & 75 BSC (*reference*)	6.3% 5.5% 5.8% NA	5.9 7.5 (5.5-12.8) [d] 7.0 (5.5-9.0) 4.6 (3.7-6.0)	19% 37% (24-50%) [d] 29% (20-38%) [d] 19% (11-28%) [d]	D100 vs. BSC100: p=0.78 log rank D75 vs. BSC75: p=0.01 log rank D vs. BSC, p=0.047 log rank	Advantage over BSC for D100&75 on pain (pts, p=0.005; obs, p=0.08) and fatigue (obs, p=0.068), and for D100 on pain (pts, p=0.003).	<u>D75 / D100:</u> Anemia, 6% / 16% Neutropenia, 67% / 86% Febrile neutropenia, 2% / 22% Septic deaths, 0% / 6% <u>D75 / D100 / BSC:</u> Asthenia, 18% / 22% / 28% Infection, 6% / 14% / 5% Pulmonary, 20% / 37% / 30% Toxic deaths, 2% / 10% / NA
Fossella 2000 (17,22) (TAX 320)	Docetaxel 100 Docetaxel 75 Vinorelbine / Ifosfamide	10.8% 6.7% 0.8% D100 / D75 versus Vinorelbine/ Ifosfamide p<0.05	5.5 5.7 5.6	21% (14-28%) 32% (23-40%) 19% (12-26%)	Not significantly different	Advantage for D100 over vinorelbine/ifosfamide (p<0.05) on total scores (pts & obs), fatigue (pts), symptom distress (pts), and pain (obs). General trend reported in favour of D100&75.	<u>D100 / D75 / Vinorelbine or Ifosfamide:</u> Neutropenia, 77% / 54% / 31% Febrile neutropenia, 12% / 8% / 1% Filgrastim, 28% / 7% / 3% cycles Neurosensory, 6% / 1% / 3% Asthenia, 17% / 12% / 11% Nausea/vomit, 7% / 1-3% / 4-6% Discontinuation due to toxicity, 13% / 7% / 4%. Toxic deaths, 2% / 0% / 2%
Hanna 2004 (21) (JMEI)	Docetaxel *(reference)* Pemetrexed	8.8% 9.1% p=NS	7.9 8.3	29.7% 29.7%	HR 0.99 95% CI, 0.82-1.2 p=0.226 [e] Percent retention method, p=0.047	No significant differences in symptom burden on pts (p=0.1447) or obs ratings.	<u>D75 / Pemetrexed"</u> Neutropenia, 40% / 5% Febrile neutropenia, 13% / 2% Hospitalizations for infection (>1), 13% / 2% G-CSF, 19% / 3% , all p<0.001 Non-hematologic, infrequent. Treatment-related deaths, 2% / 1%
Ramlau 2005 [f] (23,24) (387)	Docetaxel *(reference)* Topotecan	4.6% 4.6%	7.1 (6.3-7.8) 6.4 (5.5-7.2)	28.7% (24-33) 25.1% (21-29)	HR 1.16 95% CI, 1.00-1.35 p=0.057 log rank [e]	Advantage for docetaxel over topotecan (p<.0001)	<u>Docetaxel/Topotecan</u> Neutropenia, 60% / 50% Anemia, 10% / 26% Thrombocytopenia, 7% / 26%

Abbreviations: BSC = best supportive care, CI = confidence interval, CR = complete response, D = docetaxel, HR = hazard ratio, NA = not applicable, NS = not statistically significant, obs = observer scale, pts = patient scale, PR = partial response, vs. = versus.

[a] Treatment regimens are described in detail in Appendix C.

[b] Response rate was based on the intent-to-treat population (16) or patients given at least one chemotherapy infusion: 358 patients (17) and 538 patients (21).

[c] Quality of life assessed using the Lung Cancer Symptom Scale (16,17,21,23) or the European Organization for Research and Treatment of Cancer scales (16).

[d] Data obtained through personal communication with Dr. F. Shepherd.

[e] Non-inferiority test.

[f] Abstract.

Median survival for D75 was 7.5 months compared to 4.6 months for BSC, with one-year survival of 37% versus 19% (p=0.01 log rank), respectively. This survival benefit was seen despite a low overall tumour response rate (RR)) of 5.8% in both treatment arms. The incidence of febrile neutropenia was significantly higher for D100 than for D75, with grade 3/4 in 22% of patients (including three deaths) versus 2% (with no deaths), respectively. However, non-hematologic toxicities were similar for both treatment groups. The median number of chemotherapy cycles delivered was significantly lower for D100 than for D75, at two versus four cycles.

The QOL analysis for the TAX 317 trial was reported separately by Dancey et al (20). Comparison of QOL changes revealed a significant difference in mean patient-rated pain scores favouring the combined docetaxel treatment arms over BSC (p=0.005) and trends in favour of treatment for observer-rated scales for fatigue and pain. In separate comparisons of D100 versus BSC100 and D75 versus BSC75, D100 (but not D75) showed significant benefits over BSC in mean patient-related pain scores (p=0.003), and trends in favour of docetaxel for observer-rated total Lung Cancer Symptom Scale (LCSS) score (p=0.094), appetite (p=0.098), and fatigue (p=0.092).

In the TAX 320 randomized phase III trial, two dose levels of docetaxel, 100 mg/m^2 and 75 mg/m^2 administered three-weekly (D100 and D75), were compared with a control arm of vinorelbine or ifosfamide (V/I), with the control treatment chosen by the investigator (17). Treatment was continued for six or more cycles in patients with response or stable disease in the absence of unacceptable toxicity. Comparison of each docetaxel arm versus V/I showed no statistically significant difference in overall survival between the treatment groups. However, comparison of one-year survival rates (post-hoc) revealed a significant benefit for D75 over V/I (32% versus 19%, p=0.025, chi-square). Once again, the RR with each treatment was relatively modest, although significantly higher for both docetaxel arms than for V/I. The median number of cycles of chemotherapy administered was three in both docetaxel arms, three in the vinorelbine arm, and two in the ifosfamide arm. Approximately one-third of patients received additional chemotherapy following study treatment (including 15% of patients in the control arm who subsequently received docetaxel). In order to explore the potential impact of crossover treatment on survival, comparisons were made both with (post-hoc) and without censoring at the time of additional post-study treatment. After censoring, the overall survival difference remained non-significant for D100 versus V/I (p=0.13 log rank), and for D75 versus V/I (p=0.12 log rank), although the one-year survival rates for both docetaxel arms became statistically superior to the control arm (32% versus 10%, p=0.001 chi-square and p=0.002 chi-square, for D100 and D75 arms, respectively). Both survival and RR were reported as similar regardless of prior treatment with paclitaxel. The incidence of febrile neutropenia was considerably higher in the docetaxel arms, but was not associated with an excess of treatment-related deaths in the D100 arm, as seen in the TAX 317 trial (16). Grade 3-4 non-hematologic toxicities were infrequent and occurred with similar incidence in all three treatment groups.

Results of QOL analyses from the TAX 320 trial have yet to be fully reported. In an abstract report, Miller et al reported a benefit for docetaxel over V/I, particularly the D100 arm, on a number of QOL scores, including patient-rated total score, fatigue, and total symptomatic distress, and observer-related total score and pain (22).

The JMEI randomized phase III trial, conducted by Eli Lilly, was designed to test for non-inferiority with respect to survival of pemetrexed at a dose of 500 mg/m^2 versus docetaxel at 75 mg/m^2 each, administered on a three-weekly schedule, as second-line treatment (21). Patients assigned to pemetrexed also received vitamin supplementation with folic acid plus vitamin B_{12} for the duration of treatment. Treatment was continued until

disease progression or unacceptable toxicity. Median follow-up for all patients was 7.5 months, and 71.6% of patients had died by the time of the analysis.

The primary test for non-inferiority, which required that survival with pemetrexed be ≤10% worse than with docetaxel (corresponding to a true hazard ratio [HR] of 0.83 and an upper 95% confidence limit [CI] of <1.11 for pemetrexed over docetaxel), was not met (HR 0.99; 95% CI 0.82 to 1.2; non-inferiority p=0.226). However, a second pre-planned test of non-inferiority (percent retention method), which required that pemetrexed retain ≥50% of the survival benefit of docetaxel over BSC observed in the TAX 317 trial (16), was statistically significant (102% survival benefit retained with a lower 95% confidence limit of 52%, p=0.047). Survival was also shown to be similar for both treatment groups (HR 0.93; 95% CI 0.76-1.13; non-inferiority p=0.051) after adjusting for variables associated with increased survival (PS, disease stage, and time since last chemotherapy) in a multiple regression analysis. The median number of cycles of chemotherapy administered was four in both groups.

Approximately 42% of patients received additional chemotherapy following study treatment, including 47% of patients in the pemetrexed arm (two thirds of whom received docetaxel) and 37% in the docetaxel arm. In order to assess the potential impact of that treatment crossover on the test of non-inferiority, an exploratory analysis was performed of patients who went on to receive subsequent chemotherapy. In that analysis, the median survival of pemetrexed patients who subsequently received docetaxel (n=85, 9.6 months) appeared to be no better than that of patients who received other chemotherapy agents post-study (n=41, 10.6 months, p=0.219) (21,51), arguing against a substantial impact of crossover from pemetrexed to docetaxel on the survival analysis.

The incidence of febrile neutropenia, infections, and hospitalizations due to neutropenic events was significantly higher for docetaxel than for pemetrexed, but treatment-related deaths and non-hematologic toxicities, occurred with similar frequency in both arms. Quality of life assessments indicated no significant differences between the treatment groups.

The 387 randomized phase III trial, was designed to test the non-inferiority of oral topotecan at a dose of 2.3 mg/m^2/d on days 1-5 versus IV docetaxel at 75 mg/m^2, each administered on a three-weekly schedule (23,24), as second-line therapy. Treatment was continued for at least four cycles or until disease progression.

The test for non-inferiority, which required that the one-year survival rate with topotecan be less than 10% worse than with docetaxel, was met. The one-year survival for topotecan was 25.1% (95% CI 20.9-29.3) compared to 28.7% for docetaxel (95% CI 24.3-33.0), corresponding to an absolute difference of 3.6% (95% CI -9.6% to +2,5%). The overall survival was not statistically significant between treatment groups, but showed a trend in favour of docetaxel (HR 1.16; CI 1.00-1.35, log-rank p = 0.057), with median survival (MS) of 27.9 weeks and 30.7 weeks for topotecan and docetaxel, respectively. The median number of cycles of chemotherapy administered was four in the docetaxel arm and three in the topotecan arm (23,24). Approximately 28% of patients received additional chemotherapy following study treatment, including 31% of patients in the topotecan arm and 25% in the docetaxel arm.

The pattern of grade 3-4 toxicities differed by treatment arm. The incidence of neutropenia and sepsis was higher for docetaxel, whereas anemia and thrombocytopenia were more frequent with topotecan. Grade 3-4 non-hematologic toxicities were infrequent but included more frequent neuropathy for docetaxel and a higher incidence of nausea for topotecan. Quality of life assessments were significantly higher for the docetaxel arm when compared to topotecan (p <0.0001, Wilcoxon rank-sum test). The rate of change from baseline of individual LCSS scores in the slope analysis also favoured docetaxel, although the only significant difference seen was for appetite, which was perhaps attributable to pre-medication with dexamethasone.

Single-agent docetaxel - dose and schedule comparisons

Docetaxel administered at a dose of 75 mg/m^2 every three weeks is associated with a significant risk of both hematologic and non-hematologic toxicities, including grade 3/4 neutropenia (40-67%), febrile neutropenia (2-13%), grade 3/4 asthenia (5-18%), and alopecia (35-38%) (16,17,21,23,24). Phase I testing of lower doses of docetaxel administered weekly for six consecutive weeks on an eight-week cycle to patients with advanced refractory cancer demonstrated a lower incidence of grade 3/4 neutropenia and febrile neutropenia, and promising overall tolerability (52).

Four randomized trials, including three phase III and one phase II trial, have compared three-weekly with weekly administration of single-agent docetaxel as second-line or subsequent therapy for relapsed/progressive NSCLC (25-29). These trials are summarized in Tables 3a and 3b. One of the phase III trials (25,26) was reported in abstract form only and provided limited data on the trial methods. None of the trials reported blinding of treatment assignment for researchers or patients. In one phase III trial (DISTAL-01) the method of randomization, and basis for deciding sample size were described (27). That trial was somewhat unusual, in that sample size was based upon QOL as a primary endpoint. In the second phase III trial, sample size was based upon a test of equivalence for survival (28). In the third phase III trial, the method of randomization and basis for sample-size determination were unclear, although survival was described as the primary endpoint (25,26). Stratification variables differed for each of the phase III trials; however, two included stratification by PS (25-27). The phase II trial was explicitly described as non-comparative for efficacy outcomes and included a primary outcome of safety, specifically the incidence of grade 3/4 neutropenia, febrile neutropenia, nausea/vomiting, and asthenia (29).

Table 3a: Trials of single-agent docetaxel comparing different dose or schedule combinations: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]			
			Prior Therapy		Disease Stage	PS [e]
			Platin	Taxane [d]	III/IV	0-1 / 2
Randomized phase III trials (weekly versus three-weekly)						
Camps 2003 [f] (25,26)	D75 q3wkly	91	88	16	NR	83 / 17
	D36 qwkly (6 of 8)	88	85	22		84 / 17
Gridelli 2004 (27) (DISTAL-01)	D75 q3wkly	110	85	NR	19 / 81	85 / 15
	D33.3 qwkly (6 of 8)	110	84		9 / 91	84 / 16
Schuette 2005 (28)	D75 q3wkly	103	NR	23	NR	86 / 12
	D35 qwkly (3 of 4)	105 [g]		26		86 / 11
Randomized phase II trials (weekly versus three-weekly)						
Gervais 2005 (29)	D75 q3wkly	62	100	0	34 / 66	79 / 21
	D40 qwkly (6 of 8)	63	100	0	33 / 67	79 / 21
Randomized phase II trials (other)						
Quoix 2004 (30)	D100 q3wkly	89	100	0	21 / 79	78 / 23
	D75 q3wkly	93	100	0	9 / 91	74 / 26

Abbreviations: D = docetaxel, NR = not reported, PS = performance status, q = every, wkly = weekly.

[a] Treatment regimens are described in detail in Appendix C.

[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.

[c] Where reported, trials allowed for the inclusion of patients with central nervous system metastases which were stable and/or asymptomatic (25-27,29,30)

[d] Prior taxane allowed was paclitaxel (25,26,28).

[e] Based on the Eastern Cooperative Oncology Group scale (27,28), World Health Organization scale (29,30), or scale not reported (25,26).

[f] Abstract

[g] The total number of randomized patients was 215 (28).

Table 3b: Trials of single-agent docetaxel comparing different dose or schedule combinations: trial outcomes.

Reference	Treatment [a]	Response Rate (CR + PR) [b]	Survival			Qualify of Life [c]	Common grade 3 or 4 Toxicity (>5% of Pts)
			Median, Months (95% CI)	1-year (95% CI)	Overall		
Randomized phase III trials (weekly versus three-weekly)							
Camps 2003 [d] (25,26,53)	D75 q3wkly D36 qwkly (6 of 8)	11% 9%	6.3 (5.2-7.5) 6.1 (4.5-7.7)	NR	p=0.2036	Not significantly different between treatment arms [f]	q3wkly / q1wkly: Neutropenia, 9% / 2% (febrile, 1% / 1%) Anemia, 3% / 6% Asthenia, 12% / 11% Dyspnea, 2% / 9% Anorexia, 3% / 6% Mucositis, 2% / 7% Diarrhea, 1% / 5%.
Gridelli 2004 (27) (DISTAL-01)	D75 q3wkly D33.3 qwkly (6 of 8)	2.7% 5.5% p=0.50	6.7 (4.8-8.3) 5.8 (4.2-7.8)	21% 31%	HR 1.04 [e] 95% CI, 0.77-1.39 p=0.80	No significant differences on global or functioning scales. Advantage for D qwkly at 3 weeks for cough (p=0.007) and hair loss (p=<0.0001).	q3wkly / q1wkly: Neutropenia, 19% / 2%, p<0.0001 Febrile neutropenia,5% / 0%, p=0.03 Fatigue, 7% / 6%
Schuette 2005 (28)	D75 q3wkly D35 qwkly (3 of 4)	12.6% 10.5%	6.3 (4.7-7.8) 9.2 (5.8-12.6)	26.9% 39.5%	p=0.07	Not significantly different between treatment arms	q3wkly / q1wkly: Neutropenia, 21% / 5%, p≤0.001 Febrile neutropenia, 2% / 1% Anemia, 6% / 1%, p≤0.05 Leukopenia, 28%/1%, p<0.0001 Nausea/vomiting, 5% / 7% Pain, 12% / 9% Pulmonary, 10% / 4% Nail changes, 4% / 8%
Randomized phase II trials (weekly versus three-weekly)							
Gervais 2005 (29)	D75 q3wkly D40 qwkly (6 of 8)	4.8% 3.2%	5.8 5.5	18% 6%	NR	NR	q3wkly / q1wkly: Neutropenia, 48% / 16%, p=0.0001 [f] Febrile neutropenia, 7% / 0% Anemia, 10% / 13% Asthenia, 5% / 11% Discontinuation due to toxicity, 5% / 13%

Randomized phase II trials (other)							
Quoix 2004 (30)	D100 q3wkly D75 q3wkly	7.6% 8.6%	6.7 (4.8-7.1) 4.7 (3.8-5.9)	NR	NR	NR	D100 / D75: Neutropenia: 73% / 44% Febrile neutropenia, 7% / 7% Anemia, 15% / 12% Fatigue/asthenia, 19% / 9% Nausea/vomiting, 8% / 5% Infection, 6% / 0% Treatment-related deaths, 3% / 3%

Abbreviations: CI = confidence interval, CR = complete response, D = docetaxel, HR = hazard ratio, NR = not reported, PR = partial response, Pts = patients, q = every, wkly = weekly.

[a] Treatment regimens are described in detail in Appendix C.

[b] Basis for calculation of response rate is the intent-to-treat population (27,29), 207 (28) completing study treatment, 160 response evaluable patients (30), 150 patients (25,26).

[c] Quality of life assessed using the Lung Cancer Symptom Scale (53), the European Organization for Research and Treatment of Cancer scales (27,28), or daily diary cards (27).

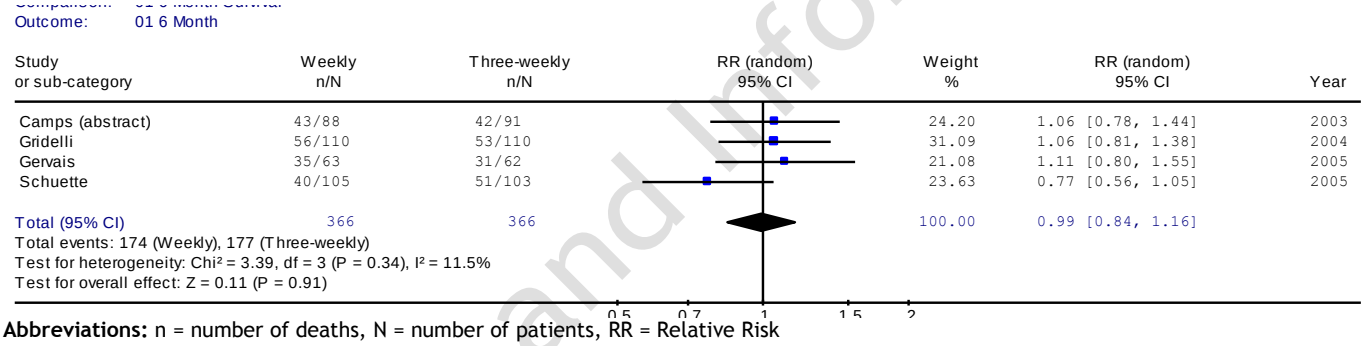
[d] Abstract

[e] Hazard ratio obtained from Cox model adjusted for PS, age, sex, disease stage, previous cisplatin use, and response to first-line treatment.

[f] Assessed for 103 patients

None of the four trials comparing weekly with three-weekly administration of docetaxel, reported a statistically significant difference in median survival between schedules. One trial reported a difference in median survival between schedules that approached statistical significance, and favoured the weekly arm (6.3 months versus 9.2 months, p=0.07) (28). A pooled analysis of survival data from the randomized trials of weekly (33.3-40 mg/m^2) versus three-weekly (75 mg/m^2) docetaxel schedules was performed. Survival rates at six months were extrapolated for these trials from published survival curves, as reported in slide presentations (26) or fully published articles (27-29). Six months was chosen as the time-point for pooling survival data, because that was prior to the weighted median survival calculated for all studies (6.3 months) and would, therefore, be expected to include data from a reasonable number of patients for analysis. The meta-analysis, shown in Figure 1, detected no significant survival differences between the two treatment administration schedules at six months (Relative Risk, 0.99; p=0.91) and no significant heterogeneity of treatment effects across trials (p=0.34). The limitations of that analysis are discussed in the *Synthesizing the Evidence* section of this review.

Figure 1. Meta-analysis of six-month survival for weekly versus three-weekly administration of single-agent docetaxel.

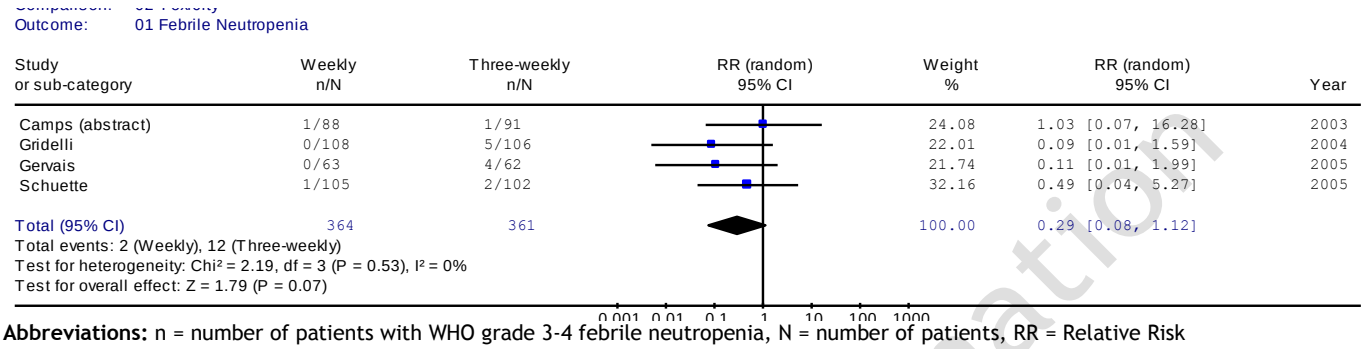


Abbreviations: n = number of deaths, N = number of patients, RR = Relative Risk

None of the four trials comparing weekly with three-weekly docetaxel administration reported a statistically significant difference in response rate between the two treatment schedules. Of the three trials that reported QOL outcomes (27,28,53), only one provided detailed data. In that trial, comparison of treatment groups showed no significant difference in mean change from baseline in global QOL at three weeks. However, significant changes from baseline were observed for the weekly schedule in several other QOL measures, including better pain control (p=0.04), cough (p=0.007), and alopecia (p<0.001) and worse diarrhea (p=0.01). The QOL response at 21 days also showed significant differences for cough (p=0.007) and alopecia (p<0.0001), favouring the weekly arm. Using daily diary cards, no statistically significant treatment differences were observed for most symptoms, with the exception of pain, which was consistently lower with the weekly schedule (p=0.04 overall, p=0.74 interaction test) (27). The other two trials found no significant difference in QOL between treatment groups (28,53).

Of the four trials comparing weekly with three-weekly administration of docetaxel, the majority indicated a reduced risk of neutropenia and febrile neutropenia for docetaxel administered weekly versus three-weekly (25-29). A meta-analysis of the incidence of febrile neutropenia for weekly versus three-weekly docetaxel schedules was conducted (Figure 2). The difference in incidence of grade 3/4 febrile neutropenia approached, statistical significance (Relative Risk, 0.29; p=0.07), with no significant heterogeneity of treatment effect.

Figure 2. Meta-analysis of febrile neutropenia for weekly versus three-weekly administration of second-line or subsequent docetaxel



Abbreviations: n = number of patients with WHO grade 3-4 febrile neutropenia, N = number of patients, RR = Relative Risk

An additional published randomized phase II trial compared two different doses of docetaxel (100 mg/m^2 versus 75 mg/m^2), both administered every three weeks (30). Median survival was 6.7 months for docetaxel 100 mg/m^2, and 4.7 months for docetaxel 75 mg/m^2. An imbalance in the proportion of patients with stage IV disease assigned to each treatment group may have contributed to these results. The incidence of grade 3/4 neutropenia was higher with docetaxel 100 mg/m^2 but did not result in more frequent febrile neutropenia in the higher dose arm. The incidence of grade 3/4 non-hematologic toxicities was similar in both treatment arms, with the exception of asthenia, diarrhea, and infections, which occurred more frequently with docetaxel 100 mg/m^2.

Docetaxel-based combination chemotherapy comparisons

Docetaxel-based combination chemotherapy regimens have been compared to single agents or other combination regimens as second-line or subsequent therapy for relapsed/progressive disease in four randomized trials, three phase II, and one phase III (31-37). Of those trials, summarized in Tables 4a and 4b, two were reported in abstract form only. One of the trials reported receiving industry support (34). None reported blinding of treatment assignment for researchers or patients or described the randomization process in detail. The primary outcome was RR in two trials (33,34) and survival in two trials (31,32,35-37), although only one trial described the method used for sample size estimation (31,32).

A randomized phase III trial of the Japanese Clinical Oncology Group (JCOG 0104), reported in abstract form only, compared docetaxel plus gemcitabine with single-agent docetaxel (31,32). Planned enrolment for that study was 284 patients; however, accrual was halted prematurely at 130 patients, after an unexpectedly high incidence of interstitial lung disease (ILD) was observed in the combination arm. Grade 2-4 pneumonitis was seen in 16.9% of patients receiving docetaxel plus gemcitabine compared to 1.6% for single-agent docetaxel, with fatal pneumonitis occurring in 4.6% of patients in the combination arm. No baseline risk factor, other than male gender, was identified that predicted for development of ILD. No significant difference in survival, QOL or RR was observed between treatment arms.

Two randomized phase II trials compared docetaxel alone with docetaxel plus irinotecan (33) plus G-CSF (34). One trial employed a "pick-the-winner" statistical design to determine which was the best treatment arm (34). This strategy is intended to rank outcomes, and is not equivalent to a standard statistical comparison (54). The RRs were similar across treatments in both trials, although in one trial single-agent docetaxel was

ranked the "winner" based upon a higher RR (34). No statistically significant treatment differences in survival were observed in either trial, however the trials were not powered or designed to compare survival (33,34). An additional randomized phase II trial by Lilenbaum et al., reported in abstract form only, compared a docetaxel-based combination regimen with either a single agent or another combination regimen (35-37). This trial employed a 2x2 design to compare irinotecan plus docetaxel or gemcitabine, both with and without celecoxib (43-45). Results are summarized in Table 4a and 4b.

Combination chemotherapy without docetaxel

Two small randomized phase II trials compared a non-docetaxel-based combination chemotherapy regimen with single-agent chemotherapy as second-line or subsequent therapy for relapsed/progressive NSCLC (38,39). Both trials compared an irinotecan-based combination regimen with a single agent, determined the sample size by the primary endpoint of survival with 90% power to detect a significant difference, and one reported the method of randomization (38). Neither explicitly reported the proportion of patients included in the analyses. Results are summarized in Table 5a and 5b.

The Hellenic Oncology Research Group (HORG) compared irinotecan plus gemcitabine versus irinotecan single agent (38). The RR for the combination was superior, but this did not translate into a significant survival benefit. The combination treatment demonstrated significant superiority over the single agent for several QOL parameters, including "general mood today" (p=0.014), cough (p=0.033), and "intensity of symptoms" (p=0.034), although limited information was provided on the QOL analyses. A second trial by the HORG compared cisplatin plus irinotecan versus single-agent cisplatin (39). The RR for the combination was also superior, but did not translate into improved median or one-year survival.

Table 4a: Trials of docetaxel-based combination chemotherapy: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]					
			Treatment Line	Prior Therapy		PD with prior CT	Disease Stage	PS [e]
			2nd/3rd/4th+	Platin	Taxane[d]		III/IV	0-1 / 2
Randomized phase III trials								
Takeda 2004 [f] (31,32)	Docetaxel	65	100 / 0	100	NR	8	NR	100 / 0
	Docetaxel + Gemcitabine	65	100 / 0	100		9		100 / 0
Randomized phase II trials								
Pectasides 2005 (33)	Docetaxel	65	100 / 0 / 0	100	47	NR	NR	88 / 12
	Docetaxel + Irinotecan	65	100 / 0 / 0	100	47			84 / 16
Wachters 2005 (34)	Docetaxel	56	NR	71	NR	NR	25 / 75	88 / 13
	Docetaxel + irinotecan + G-CSF	52		75			21 / 79	96 / 4
Lilenbaum 2005 [f] (35-37)	Irinotecan + Docetaxel +/- Celecoxib (ID)	69	100 / 0 / 0	NR	NR	32	NR	100 / 0
	Irinotecan + Gemcitabine +/- Celecoxib (IG)	64	100 / 0 / 0			33		99 / 1
	Celecoxib + ID or IG (+Cbx)	67	100 / 0 / 0			35		99/1
	No Celecoxib + ID or IG (-Cbx)	66	100 / 0 / 0			29 [g]		100/0

Abbreviations: CT = chemotherapy, G-CSF = granulocyte-colony stimulating factor, NR = not reported, PD = progressive disease, PS = performance status.

[a] Treatment regimens are described in detail in Appendix C.

[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.

[c] Where reported, trials allowed for the inclusion of patients with CNS metastases which were stable and/or asymptomatic (34-37).

[d] Prior taxane allowed was paclitaxel (33) and docetaxel was not allowed in two trials (31-33).

[e] Based on the Eastern Cooperative Oncology Group scale (31-37).

[f] Abstract

[g] Proportion of patients reported as resistant to prior chemotherapy.

Table 4b: Trials of docetaxel-based combination chemotherapy: trial outcomes.

Reference	Treatment [a]	Response Rate (CR + PR)[b]	Survival Median, Months (95% CI)	Survival 1-year (95% CI)	Survival Overall	Qualify of Life [c]	Common grade 3 or 4 Toxicity (>5% of Patients)
Randomized phase III trials							
Takeda 2004 [d] (31,32)	Docetaxel	6.7%	10.1 (7.4-12.6)	41.9% (29.0-54.9)	HR 0.91 95% CI, 0.59-1.41 p=0.68 log rank	Similar decreases in both treatment arms between baseline and week 6 (p=0.614).	Docetaxel / Docetaxel-gemcitabine: Neutropenia, 86% / 77% Febrile neutropenia, 22% / 15% Anemia, 3% / 15% Thrombocytopenia, 0% / 12% Infection, 3-8% / 15% ALT elevation, 2% / 8% Pneumonitis (ILD), 0% / 12% (5% deaths)
	Docetaxel + Gemcitabine	7.0% p=0.94	10.2 (6.5-14.7)	45.6% (33.1-58.1)			
Randomized phase II trials							
Pectasides 2005 (33)	Docetaxel	14%	6.4 (0.1-21.2)	34%	p=0.49 log rank	Equivalent clinical benefit (cough, pain, dyspnea, hemoptysis, anorexia, fatigue, PS) in both treatment arms	Docetaxel / Docetaxel-irinotecan: Neutropenia, 43% / 46% Febrile neutropenia, 5% / 5% Anemia, 12 % / 23% Thrombocytopenia, 6% / 17%, p=0.04 Nausea/vomiting, 8% / 17% Diarrhea, 3% / 12%, p=0.05 Fatigue/asthenia. 14% / 14% Alopecia, 85% / 52% Treatment related deaths, 2% / 0%
	Docetaxel + Irinotecan	20% p=0.36	6.5 (0.4-22.2)	37% p=0.72			
Wachters 2005 (34)	Docetaxel	16%	7.4 (5.8-9.2)	26%	p=0.69 log rank	NR	Docetaxel / Docetaxel-irinotecan: Neutropenia, 43% / 22% Febrile neutropenia, 5% / 6% Anemia, 0% / 10% Diarrhea, 2% / 14% Treatment-related deaths, 2% / 4%
	Docetaxel + irinotecan + G-CSF	10%	6.2 (1.8-10.6)	30%			
Lilenbaum 2005[d] (35-37)	Irinotecan + Docetaxel +/- Celecoxib (ID)	3%	6.4	21%	NR	Similar proportion of patients experienced improvement in all treatment groups.	ID / IG / +Cbx / -Cbx:[e] Neutropenia, 6% / 3% / 7% / 2% Thrombocytopenia, 0% / 5% / 4% / 0% Anemia, 3% / 5% / 7% / 0% Nausea/vomiting, 9-12% / 5-6% / 9-10% / 5-8% Diarrhea, 33% / 9% / 19% / 24%
	Irinotecan + Gemcitabine +/- Celecoxib (IG)	6%	8.9	40%			
	Celecoxib + ID or IG (+Cbx)	3%	6.3	24%			
	No Celecoxib + ID or IG (-Cbx)	6%	9.2	36%			

Abbreviations: ALT = alanine aminotransferase, CI = confidence interval, CR = complete response, G-CSF = granulocyte-colony stimulating factor, HR = hazard ratio, ILD = interstitial lung disease, NR = not reported, PR = partial response, PS = performance status.

[a] Treatment regimens are described in detail in Appendix C.
[b] Basis for calculation of response rate is randomized or eligible patients (33,34), 133 patients receiving at least one treatment (35-37), or 117 treated and eligible patients with measurable lesions (31,32)
[c] Quality of life assessed using the Functional Assessment of Cancer Therapy – Lung (31,32), the Lung Cancer Symptom Scale (35-37) or an un-validated, local scale (33).
[d] Abstract.
[e] Toxicity data reported in WCLC abstract

Table 5a: Trials of combination chemotherapy without docetaxel: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]				
			Treatment Line	Prior Therapy		Disease Stage III/IV	PS [e]
			2nd/3rd/4th+	Platin	Taxane [d]		0-1 / 2
Randomized phase II trials							
Georgoulias 2004 (38)	Irinotecan	71	100 / 0 / 0	100	100	0 / 100	90 / 10
	Irinotecan + Gemcitabine	76	100 / 0 / 0	100	100	0 / 100	91 / 9
Georgoulias 2005 (39)	Cisplatin	73	90 / 10 / 0	NR	100	0 / 100	78 / 22
	Cisplatin + Irinotecan	74 [f]	96 / 4 / 0		100	0 / 100	82 / 18

Abbreviations: NR = not reported, PS = performance status.
[a] Treatment regimens are described in detail in Appendix C.
[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.
[c] None of the trials reported if patients with CNS metastases were included.
[d] Prior taxane was docetaxel and paclitaxel (39) or docetaxel (38).
[e] Based on the World Health Organization scale (38,39)
[f] Seven of the 154 randomized patients were excluded from the analyses because of a major protocol violation, failure to receive study treatment, or administration of radiotherapy

Table 5b: Trials of combination chemotherapy without docetaxel: trial outcomes.

Reference	Treatment [a]	Response Rate (CR + PR) [b]	Survival			Qualify of Life [c]	Common grade 3 or 4 Toxicity (>5% of Pts)
			Median, Months (95% CI)	1-year (95% CI)	Overall		
Randomized phase II trials							
Georgoulias 2004 (38)	Irinotecan	4.2%	7	29%	p=0.589 log rank	Trend favoured combination treatment but participation (% patients) was limited: Baseline, 73%, Cycle 3, 54% Cycle 6, 24%	Irinotecan / Irinotecan-Gemcitabine: Neutropenia, 18% / 28%, p=0.180 Febrile neutropenia, 11% / 4%, p=0.092 Anemia, 0% / 8%, p=0.029 Thrombocytopenia, 3% / 9%, p=0.106 Nausea/vomiting, 4% / 7% Diarrhea, 23% / 16% Asthenia, 13% / 8%
	Irinotecan + Gemcitabine	18.4% p=0.009	9	24.5%			
Georgoulias 2005 (39)	Cisplatin	7.0%	8.8	31.7%	p=0.934 log rank	No significant difference between treatment arms on qualify of life measures	Cisplatin / Cisplatin-Irinotecan: Neutropenia, 4% / 31%, p=0.001 Anemia, 2% / 6% Thrombocytopenia, 3% / 7% Nausea/vomiting, 4% / 12%, p=0.083 Diarrhea, 4% / 27%, p=0.0001 Asthenia, 13% / 11%
	Cisplatin + Irinotecan	22.5% p=0.012	7.8	34.3%			

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response, Pts = patients.
[a] Treatment regimens are described in detail in Appendix C.
[b] 134 patients evaluable for response (39) or 147 patients evaluable for response (38).
[c] Quality of life assessed using the Lung Cancer Symptom Scale (38,39), the EuroQOL scale (38,39)

Novel Systemic Agents

Epidermal growth factor receptor inhibitors (EGFR-I)

A number of growth-factor-receptor-targeted agents have been tested in the second-line or subsequent therapy of relapsed/progressive NSCLC. Those include two agents for which randomized phase II or phase III data are currently available. Both agents are oral formulation small-molecule receptor tyrosine kinase inhibitors targeting the epidermal growth factor receptor, namely, erlotinib (Tarceva®) and gefitinib (Iressa®).

Two double-blind randomized phase III trials have compared gefitinib or erlotinib with placebo (40,41). Both trials involved multiple centres and enrolled patients internationally. Two published randomized phase II trials evaluated different daily doses of gefitinib, one performed in the U.S. (19) and the other was multinational (18). One randomized phase II trial, performed in Europe and reported in abstract form, evaluated docetaxel alongside gefitinib (42,43). All five of those trials, summarized in Tables 6a and 6b, received industry support. A detailed description of the method of randomization was lacking for several of the trials, although three specified that randomization was performed centrally (18,40,41). Four trials described the basis for estimation of trial sample size and met their target accrual (18,19,40,41). The randomized phase II trials were not designed to compare outcomes between treatment groups (18,19,42,43).

Single-agent Erlotinib compared with BSC

A double-blind randomized phase III trial conducted by the National Cancer Institute of Canada Clinical Trials Group (BR.21), assigned patients in a 2:1 ratio to erlotinib at a dose of 150 mg daily or placebo (40). Treatment was continued until disease progression or unacceptable toxicity. The study was initially powered to detect a 50% improvement in median survival. However, the sample size was adjusted before analysis, to provide power to detect a 33% improvement in median survival (55). Collection of tumour samples for tissue banking and correlative studies was optional.

Comparison of survival outcomes revealed a significant survival benefit for erlotinib over placebo, after adjustment for stratification factors (except centre) and EGFR status. The MS was 6.7 months for the erlotinib arm versus 4.7 months for placebo (adjusted HR 0.70; log-rank $p<0.001$), with one-year survival rates of 31% and 22%, respectively. RR was 9% for erlotinib compared to <1% for placebo ($p<0.001$). Analysis of clinical predictors of response to erlotinib suggested a higher response rate for patients of female gender, Asian ethnicity, adenocarcinoma histology, and a history of never smoking, although only adenocarcinoma histology ($p=0.01$) and a history of never smoking ($p<0.001$) were significantly associated with response in a multivariate analysis. Factors associated with longer survival in a multivariate analysis, included treatment with erlotinib ($p=0.002$), Asian origin ($p=0.01$), adenocarcinoma ($p=0.004$), and non-smoking history ($p=0.0048$). Analysis for predictors of survival benefit indicated that erlotinib had a beneficial effect in most subgroups and the only factor that predicted differential survival benefit for erlotinib therapy was smoking history . A similar survival benefit was found for both second- and third-line patients (adjusted HR, of 0.8; 95% CI, 0.6-1.0 for both) (40).

Table 6a: Trials of EGFR-I: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]									
			Treatment Line $2^{nd}/3^{rd}/4^{th}+$	Prior Therapy Platin	Prior Therapy Taxane	PD with prior CT	Disease Stage III/IV	PS [d] 0-1 / 2	Female / Male	Smoker / Never Smoker	Asian / Non-Asian Ethnicity	Adeno / Non-adeno
Randomized phase III trials - single agent												
Shepherd 2005 (40) (BR.21)	Erlotinib	488	50 / 49 / 1	92	NR	28	NR	65 / 26	35 / 65	73 / 21	NR	50 / 50
	Placebo	243	50 / 49 / 1	92		28		68 / 23 [f]	34 / 66	77 / 17		49 / 51
Thatcher 2005 (41) (ISEL)	Gefitinib	1129	49 / 50 / 1	96	NR	38	31 / 54	65 / 29	33 / 67	78 / 22	21 / 79	48 / 52
	Placebo	563	49 / 50 / 1	96		40	26 / 56	68 / 26 [g]	33 / 67	78 / 22	19 / 81	48 / 52
Randomized phase II trials - single agent												
Fukuoka 2003 (18) (IDEAL 1)	Gefitinib 250mg	104	56 / 44 / 0	100	NR	NR	22 / 78	88 / 12	25 / 75	NR	50 / 50	64 / 36
	Gefitinib 500mg	106	57 / 43 / 0	100			17 / 83	87 / 13	34 / 66		48 / 52	67 / 33
Kris 2003 (19) (IDEAL 2)	Gefitinib 250mg	102	0 / 40 / 58	100	100	79	15 / 85	81 / 19	41 / 59	NR	0 / 100	69 / 31
	Gefitinib 500mg	114 [h]	0 / 42 / 58	100	100 [i]	total	8 / 92	79 / 20	45 / 55		0 / 100	64 / 36
Cufer 2005 [e] (42,43) (SIGN)	Gefitinib	68	97 / NR / NR	91	NR	NR	40 / 60	63/37	69/31	NR	NR	NR
	Docetaxel	73	99 / NR / NR	96			44 / 56	71/29	70/30			

Abbreviations: Adeno = adenocarcinoma, CNS = central nervous system, CT = chemotherapy,

[a] Treatment regimens are described in detail in Appendix C.

[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.

[c] Where reported, trials allowed for the inclusion of patients with CNS metastases which were stable and/or asymptomatic (18,19,40).

[d] Based on the Eastern Cooperative Oncology Group scale (40) or the World Health Organization scale (18,19,41).

[e] Abstract

[f] Both groups also included 9% of patients with PS = 3.

[g] Both groups also included 5% of patients with PS = 3

[h] Five of the 221 randomized patients were excluded from analyses (four at 250 mg and one at 500 mg) because no gefitinib was administered.

[i] All patients previously received cisplatin or carboplatin and docetaxel given concurrently or separately.

Table 6b: Trials of EGFR-I: trial outcomes.

Reference	Treatment [a]	Response Rate (CR + PR) [b]	Survival Median, Months (95% CI)	Survival 1-year (95% CI)	Survival Overall	Qualify of Life (QOL) [c] or Symptom Control	Common grade 3 or 4 Toxicity (>5% of Patients)
Randomized phase III trials - single agent							
Shepherd 2005 (40) (BR.21)	Erlotinib Placebo	9% <1% p<0.001	6.7 4.7	31% 22%	HR 0.70, p<0.001 [e]	Improvement greater with erlotinib: Pain (p=0.01), Dyspnea (p=0.03), Cough (p<0.01), Overall physical function (p=0.01) Overall emotional function (p=0.01) Global QOL (p<0.01). Months to symptom deterioration longer with erlotinib: Cough, 4.9 versus 3.7, adjusted p=0.04; Dyspnea, 4.7 versus 2.9, adjusted p=0.03; Pain, 2.8 versus 1.9, adjusted p=0.04.	<u>Erlotinib / placebo:</u> Fatigue, 19% / 23% Rash, 9% / 0% Infection, 2% / 5% Anorexia, 9% / 5% Diarrhea, 6% / <1% Discontinued due to toxicity, 5% / 2% Toxic deaths, 1patient / 1patient
Thatcher 2005 (41) (ISEL)	Gefitinib Placebo	8.0% 1.3% p<0.0001	5.6 5.1	27% 21%	HR 0.89, 95% CI, 0.77-1.02, p=0.087 log rank [f]	QOL improvement not significantly different Symptom improvement greater with gefitinib (p=0.019)	Gefitinib was generally well tolerated.
Randomized phase II trials - single agent							
Fukuoka 2003 (18)(IDEAL 1)	Gefitinib 250mg Gefitinib 500mg	18.4% 19.0% p=NS	7.6 (5.3-10.1) 8.0 (6.7-9.9)	35% 29%	NR	QOL improvement rate 250 versus 500: 23.9% (95% CI, 14.3-35.9) versus 21.9% (95% CI, 13.1-33.1). Symptom improvement rate for 140 patients evaluable, 250 versus 500: 40.3% (95% CI, 28.5-53.0) versus 37.0% (95% CI, 26.0-49.1).	<u>250 mg / 500 mg :</u> Rash, 1% / 7% Diarrhea, 0% / 7% Increased ALT, 2% / 6% ILD events, 0% / 2%
Kris 2003 (19) (IDEAL 2)	Gefitinib 250mg Gefitinib 500mg	12% 9% p=0.51	7 6 p=0.40 [g] Projected survival	27 24 p=0.54 [g]	NR	<u>For 250 versus 500</u> QOL improvement rate, 34% versus 23% Symptom improvement rate, 43% (95% CI, 33-53) vs. 35% (95% CI, 26-45)	<u>250 mg / 500 mg:</u> Overall, 7% / 18%, p=0.02 Skin, 0% / 4% Diarrhea, 1%/ 5% Pulmonary, 6% / 7% No ILD events Treatment-related deaths, 0% / 1%

Cufer 2005 [d] (42,43) (SIGN)	Gefitinib Docetaxel (*reference*)	13.2% 13.7%	7.5 7.1	NR	HR = 0.97 95% CI, 0.61-1.52 p=0.88	Gefitinib versus Docetaxel QOL improvement rate, 33.8% vs. 26% Symptom improvement rate, 36.8% vs. 26%	<u>Gefitinib / Docetaxel:</u> Neutropenia, 2% / 46% Leukopenia, 0% / 37% Asthenic conditions, 6% / 4% Dyspnea 9% / 6%

Abbreviations: ALT = alanine aminotransferase, CI = confidence interval, CR = complete response, HR = hazard ratio, ILD = interstitial lung disease, NR = not reported, NS = not statistically significant, PR = partial response, vs., versus.

[a] Treatment regimens are described in detail in Appendix C.
[b] Response rate assessed in 638 of 731 randomized patients (40), 1439 of 1692 randomized patients (41), 208 of 210 randomized patients (18), or 216 of 221 randomized patients (19).
[c] Quality of life and symptom control assessed using the Functional Assessment of Cancer Therapy – Lung scales (18,19,41,42) or the European Organization for Research and Treatment of Cancer scales (56).
[d] Abstract (42).
[e] Adjusted for EGFR status and stratification variables (with the exception of study centre).
[f] Adjusted for stratification variables (41)
[g] The statistical test used for these analyses was not clear.

Molecular analysis of tumour samples could be attempted for only 328 of 731 study participants (57). The analysis performed included quantification of EGFR protein expression, estimation of EGFR gene copy number, and sequencing of exons 18-21 to identify EGFR gene mutations, which was successful for only 325, 125 and 177 samples, respectively. Univariate analysis of the results suggested an association between EGFR gene amplification/polysomy, but not EGFR gene mutation, and the likelihood of response to erlotinib, although EGFR expression was the only molecular marker significantly associated with response in a multivariate analysis (p=0.03). Survival of patients with EGFR-expressing tumours (EGFR-positive), and those with EGFR gene amplification/polysomy, was longer with erlotinib than placebo, while survival for patients with EGFR-negative or non-amplified tumours was not different between treatment groups. However, neither EGFR expression, or EGFR gene mutation or copy number were significantly associated with survival benefit for erlotinib in a multivariate analysis. (57)

The QOL analysis reported for the BR.21 trial indicated a significant benefit for erlotinib in time to deterioration in several patient-reported symptoms, including; cough (adjusted p=0.04), dyspnea (adjusted p=0.03) and pain (adjusted p=0.04). Treatment with erlotinib was also associated with more frequent improvement in overall physical function (p=0.01), overall emotional function (p=0.01) and global QOL (p<0.01), compared with placebo (56). Grade 3/4 toxicities occurred with similar incidence in both treatment arms, with the exception of rash and diarrhea, which occurred more frequently with erlotinib, and infection, which occurred more frequently with placebo. Grade 3/4 pneumonitis occurred in <1% of patients in both arms.

Single-agent Gefitinib compared with BSC or other single agent

Two randomized trials, one phase III and one phase II, have included comparisons involving gefitinib. The phase II trial has been reported in abstract form only and provided limited information regarding study design and analysis (42,43).

The Iressa Survival Evaluation in Lung cancer (ISEL) phase III trial compared the EGFR-I gefitinib at a dose of 250 mg daily against placebo (41). Treatment was continued until loss of clinical benefit or unacceptable toxicity. Patients were randomized in a 2:1 ratio to gefitinib versus placebo. The study was initially powered to detect a survival difference for the subset of patients with adenocarcinoma; however, survival for the entire patient population was later added as a co-primary endpoint. An exploratory analysis of tumour biomarkers was planned. Nine hundred patient deaths were estimated as required to provide 90% power to detect the anticipated survival benefit of gefitinib in the overall population, and the analysis was performed after 969 deaths had been recorded.

Comparison of survival outcomes using the stratified log-rank test revealed no significant difference for gefitinib over placebo for the entire patient population. The median survival was 5.6 months for gefitinib versus 5.1 months for placebo (HR 0.89; 95% CI 0.77-1.02, stratified log-rank p=0.087), with one-year survival of 27% versus 21%, respectively. Comparison for the subgroup of patients with adenocarcinoma also demonstrated a non-significant trend toward improved survival, with a median survival of 6.3 months for gefitinib versus 5.4 months for placebo (HR 0.84; 95% CI 0.68-1.03, stratified log-rank p=0.089) and one-year survival of 30% versus 18%, respectively. Cox regression analysis, which adjusts for the effect of multiple predictor variables on survival, was statistically significant for the entire patient population (p=0.03) and the subgroup of patients with adenocarcinoma (p=0.033). Pre-planned subgroup analyses demonstrated a significant survival benefit for gefitinib in never-smokers (HR 0.67; 95% CI 0.49-0.92) and ethnic Asian patients (HR 0.66; 95% CI 0.48-0.91). RR for gefitinib was 8%, compared to 1% for placebo (p<0.0001) (41).

The QOL analysis reported for the ISEL trial revealed a non-significant trend toward favouring gefitinib for overall QOL (p=0.068). A statistically significant benefit for gefitinib was observed for change in symptom score, however this was too small to meet criteria for clinical relevance (41).

The Second-line Indication of Gefitinib in NSCLC (SIGN) randomized phase II trial, assigned patients to docetaxel 75 mg/m^2 three-weekly or gefitinib at 250 mg daily as second-line therapy (42,43). Treatment was continued until disease progression or unacceptable toxicity. A total of 134 patients were enrolled, with a median follow up of 9.3 months. Although no statistical analysis was reported, similar symptom improvement rates were seen in both treatment arms, with 36.8% and 26.0% of patients experiencing symptom improvement with gefitinib and docetaxel, respectively. The mean change in LCSS score from baseline to endpoint was also similar for the two treatment arms. The RR for gefitinib was comparable to that for docetaxel, at 13.2% versus 13.7%. MS was also similar for the two arms, at 7.5 months for gefitinib and 7.1 months for docetaxel (HR 0.97; 95% CI 0.61-1.52, p=0.88). Similar QOL improvement rates and changes in mean QOL score were seen for both treatments.

Gefitinib - dose comparisons

Two published randomized phase II trials evaluated gefitinib at different doses; IDEAL 1 (18) and IDEAL 2 (19). Those trials were double-blinded, of similar design, and employed gefitinib at 500 mg or 250 mg daily. However, the patient populations were distinct due to differences in ethnic mix and study eligibility criteria.

The IDEAL 1 trial enrolled patients with recurrent or refractory disease following one or two prior chemotherapy regimens (18). Approximately 50% of patients enrolled were Japanese. RR was not significantly different for the two doses, at 18-19%, and was similar for second (18%) and third-line therapy (20%). In responding patients, the majority demonstrated response by the first post-baseline assessment at four weeks. Multivariate analysis identified three factors correlated with tumour response: female gender (p=0.017), adenocarcinoma histology (p=0.021), and prior immuno/hormonal therapy (p=0.011). It is unclear if smoking history was included among the variables examined. Ethnicity (Japanese versus non-Japanese) was not predictive of response (p=0.25). MS was similar for the two treatment groups, at 7.6-8.0 months. Symptom and QOL improvement rates were also similar.

The IDEAL 2 trial enrolled patients with more advanced disease than IDEAL 1. Patients had to have received two or more prior chemotherapy regimens (including both platinum and docetaxel), have progressed or experienced unacceptable toxicity with the most recent regimen, and be symptomatic at the time of enrolment (19). RR was again not significantly different for the two doses but was approximately one-half that seen in IDEAL 1 (9-12%). RR was similar for third (8%), fourth-line (10%), or later treatment (15%) (p=0.38) but was higher for patients with adenocarcinoma compared to other histologic subtypes (13% versus 4%, p=0.046). However, multivariate analysis identified female gender as the only factor independently predictive of response (19% versus 3% for males, p=0.001). Symptom improvement was observed with similar frequency in both treatment groups and, as with IDEAL 1, occurred rapidly in patients who benefited, with the majority experiencing improvement within two weeks of starting treatment (58). Similar rates of symptom improvement were observed regardless of the number of prior chemotherapy regimens received. QOL analysis revealed similar improvements in Trial Outcome Index (TOI) and Functional Assessment of Cancer Therapy – Lung (FACT-L) total scores for both treatment groups (58).

Tumour samples from a subset of patients enrolled in the IDEAL trials, 119 of a total of 416 trial participants, were subsequently analysed for molecular markers (59,59). It is not

clear if the samples analyzed were representative of each trial population. Samples were analyzed for EGFR gene copy number, and by sequencing of exons 18-21 to identify EGFR gene mutations. RR was higher for tumours with EGFR mutations than wild type (46% versus 10%, p=0.005), but not different for tumours with EGFR gene amplification (29% versus 15%, p=0.319). However, as these trials were not placebo-controlled, it is not possible to infer a true interaction between treatment, EGFR mutation and tumour response. There was no apparent relationship between either EGFR mutation or amplification and survival.

Other novel systemic agents compared to other single agent

Several other novel systemic agents have been tested in the second-line or subsequent therapy of relapsed/progressive NSCLC. These include three agents for which randomized phase II data are currently available: specifically, the histone deacetylase inhibitors CI-994 (44,45) and pivaloyloxymethyl butyrate (Pivanex®) (46) and the reversible proteasome inhibitor bortezomib (Velcade®) (47,48). All three trials were reported in abstract form only and provided limited data on the trial methods. All three trials were industry-supported and multicentre, one performed in the U.S. (47,48) and the others internationally (44-46). The results are summarized in Tables 7a and 7b.

Other novel systemic agents - dose and schedule comparisons

One randomized phase II trial, reported in abstract form explored the dose and scheduling of epothilone analog BMS-247550 as second-line or subsequent therapy for relapsed/progressive NSCLC. This trial received industry support. The dosage of the agent was reduced twice through protocol amendments because of toxicity (grade 3 neuropathy), from 50 mg/m^2 administered three-weekly to 32 mg/m^2 administered three-weekly, versus 6 mg/m^2 administered on five consecutive days every three weeks. Only the data from the final protocol for that study are presented in Tables 7a and 7b.

Table 7a: Trials of other novel systemic agents: patient characteristics.

Reference	Treatment [a]	Number of Patients [b]	% Patients [c]			
			Prior Therapy		Disease Stage III/IV	PS 0-1 / 2
			Platin	Taxane		
Randomized phase II trials						
Von Pawel 2002 [d,f] (44,45)	Gemcitabine + Placebo	91	100	NR	Total, 83% stage IV	NR
	Gemcitabine + CI-994	89	100			
Raghunadharao 2005 [d] (46)	Pivanex® + docetaxel	288 total	100	38	NR	NR
	Docetaxel		100	38		
Fanucchi 2005 [d] (47,48)	Bortezomib	75	92	67	NR	NR
	Docetaxel + Bortezomib	80	96	70		
Randomized phase II trials - dose comparison						
Vansteenkiste 2003 [d] (49,50)	BMS-247550 x 1, q3wkly	76	100	53	NR	99 / 1
	BMS-247550 x 5, q3wkly	69 [e]	100	59		97 / 3

Abbreviations: NR = not reported, PS = performance status, q = every, wkly = weekly.
[a] Treatment regimens are described in detail in Appendix C.
[b] This column reports the number of patients randomized or randomized and eligible unless otherwise indicated.
[c] None of the trials reported whether patients with central nervous system metastases were enrolled.
[d] Abstract
[e] A total of 152 patients were randomized; however, data were reported for only 145 patients.
[f] Neoadjuvant treatment was allowed.

Table 7b: Trials of other novel systemic agents: trial outcomes.

Reference	Treatment [a]	Response Rate (CR + PR) [b]	Survival Median, Months	Survival 1-year	Common grade 3 or 4 Toxicity (>5% of Patients)
Randomized phase II trials					
Von Pawel 2002 [c] (44,45)	Gemcitabine + Placebo Gemcitabine + CI-994	3.8% 3.5%	6.1 6.2	NR	Toxicity grades not reported, although nausea (48% versus 34%), vomiting (47% versus 23%), and thrombocytopenia (31% versus 12%) were more frequent in the CI-994 treatment arm.
Raghunadharao 2005 [c] (46)	Pivanex® + docetaxel Docetaxel	1.8% 10.6%	4.6 6.4	NR	Pivanex + docetaxel / Docetaxel: Neutropenia, 35% / 35% Leukopenia 17% / 12% Dyspnoea 15% / 8% Anemia 10% / 4% Asthenia 7% / 4% Pneumonia 6% / 5%
Fanucchi 2005 [c] (47,48)	Bortezomib Docetaxel + Bortezomib	8% 9%	7.4 7.8	38.7% 33.1%	Bortezomib / Docetaxel + Bortezomib [d]: Neutropenia, 4% / 65% Anemia, 5% / 13% Thrombocytopenia, 8% / 5% Leukopenia, 0% / 13% Fatigue, 19% / 27% Dyspnea, 18% / 18% Peripheral neuropathy, 15% / 5% Dehydration, 14% / 5% Pneumonia, 7% / 12% Diarrhea, 8% / 9% Nausea/vomiting, 11% / 1-5% Constipation, 9% / 1% Neuralgia 4% / 6% Pleural effusion, 3% / 6%
Randomized phase II trials - dose comparison					
Vansteenkiste 2003 [c] (49,50)	BMS-247550 x 1, q3wkly BMS-247550 x 5, q3wkly	13% 10%	NR	NR	x 1 / x 5: Neutropenia, 26% / 14% Febrile neutropenia, 9% / 4% Fatigue, 5% / 9% Sensory neuropathy, 4% / 6% Treatment-related deaths, 3% / 3%

Abbreviations: CR = complete response, NR = not reported, PR = partial response, q = every, RA = rebeccamycin analogue, wkly = weekly.
[a] Treatment regimens are described in detail in Appendix C.
[b] Response rate based on randomized or eligible patients (49,50,60)
[c] Abstract.
[d] Abstract reported data for ≥10% of patients.

DISCUSSION

Single agent docetaxel at a dose of 75 mg/m^2 administered three-weekly has been shown to be of benefit for survival and QOL, in the second-line and subsequent treatment of recurrent or progressive NSCLC in the TAX 317 randomized phase III trial (16,20). Patients enrolled in that trial could not have received prior taxanes (paclitaxel or docetaxel); however, prior receipt of paclitaxel did not appear to compromise survival benefit in another phase III trial that compared docetaxel to other single agents (17,22).

In the JMEI randomized phase III trial of second-line therapy, single-agent pemetrexed at a dose of 500 mg/m^2 three-weekly (plus vitamin supplementation) has been shown to be non-inferior to docetaxel for survival, using one method of analysis (21). However, a second, more exacting test of non-inferiority was not satisfied. Pemetrexed was also found to be associated with less frequent hematologic toxicity than docetaxel, although the QOL achieved with each agent was not significantly different.

In the 387 randomized phase III trial of second-line therapy, oral topotecan at a dose of 2.3 mg/m^2/d day 1-5 every three weeks has been shown to be non-inferior to docetaxel for one-year survival rates (23,24). However, the overall survival difference approached statistical significance in favour of docetaxel, with an MS of 27.9 weeks versus 30.7 weeks for topotecan and docetaxel, respectively. Although different toxicity profiles were seen with each agent, QOL measures significantly favoured docetaxel.

For trials of non-inferiority, it is important to ensure that the results achieved reflect an equivalent efficacy of treatments, rather than equivalent inefficacy (61). The similarity in survival outcomes for docetaxel in TAX 317, JMEI and 387 trials (MS of 7.2- 7.9 months, and one-year survival rates of 28.7-37%) are reassuring in this regard. In addition, it is important to consider the potential impact of post-study therapy, as any cross-over would tend to lessen the difference in survival between treatments and increase the likelihood of declaring non-inferiority erroneously. In the JMEI trial, 42% of patients received additional post-study therapy, including 47% of patients in the pemetrexed arm (two-thirds of whom received docetaxel). In an exploratory analysis, patients on the pemetrexed arm who went on to receive docetaxel fared no better than patients who received other chemotherapy agents post-study (21,51), which would argue against a significant impact of cross-over to docetaxel on the survival analysis. The TTP for docetaxel and pemetrexed arms were comparable, at 3.5 versus 3.4 months (p=.721), respectively, which would also support the therapeutic equivalence of the two treatments. In the 387 trial, 28% of patients received additional post-study therapy, including 31% of patients in the topotecan arm. In the absence of further information, it is difficult to estimate the potential impact of cross-over on the survival analysis for that trial. However, the TTP for docetaxel was significantly longer than for topotecan, at 13.1 versus 11.3 weeks (p=.0196), which would further support its therapeutic superiority.

Docetaxel at a dose of 33-40 mg/m^2 administered weekly (for six consecutive weeks on an eight-week cycle, three weeks on a four-week cycle, or two weeks on a three-week cycle) has been shown to be associated with significantly less neutropenia than a dose of 75 mg/m^2 given three-weekly, in several phase III and phase II trials. However, none of the trials comparing weekly versus three-weekly docetaxel were designed or powered to test equivalence of these two schedules, and therefore, they have not been shown to have statistically equivalent efficacy. A pooled analysis of phase III and phase II trial data, including a total of 732 patients, indicates that weekly treatment is not associated with substantially poorer survival than three-weekly (pooled HR 0.99; 95% CI 0.84-1.16).

Docetaxel-based combination regimens that have included gemcitabine (31,32) or irinotecan (33,34) as the second agent, have not been found to be superior to docetaxel alone as second-line therapy. The combination of docetaxel with SGN-15 (62) has shown promising activity; however, this requires confirmation in appropriately designed phase III trials. Gemcitabine plus docetaxel has been found to be associated with a high incidence of ILD, suggesting the possibility of synergistic lung toxicity for those two agents when given concurrently (31,32). The combination of gemcitabine plus irinotecan, has demonstrated activity as second-line therapy after prior treatment with docetaxel-platinum (38), and warrants further investigation, as that regimen may have a role as second-line therapy for patients specifically excluded from previous trials of second-line docetaxel or pemetrexed (16,17,21).

In the BR.21 randomized phase III trial, the EGFR-I erlotinib, at a dose of 150 mg/day, has been shown to increase survival (MS of 6.7 months for erlotinib versus 4.7 months for BSC) and improve QOL, in the second-line and subsequent treatment of recurrent/progressive disease (40). A randomized phase III trial of the EGFR-I gefitinib (ISEL), failed to demonstrate a significant survival benefit (41). In that trial, no significant difference for gefitinib over

placebo was demonstrated for the patient population as a whole (MS of 5.6 months for gefitinib versus 5.1 months for placebo), with a trend approaching significance for patients with adenocarcinoma histology (6.3 months versus 5.4 months). Pre-planned subgroup analysis suggested a significant survival benefit for patients who were ethnic Asians or never-smokers (63). Gefitinib has also shown activity in second-line and subsequent therapy in two dose-comparative phase II trials, both in terms of tumour response and relief of disease-related symptoms (18,19).

There are several possible explanations for the apparent discrepancy between the results of BR.21 and ISEL trials. One possible factor may be a difference in patient population between the two trials. Both trials included patients who were ineligible for further chemotherapy; however, patients in the ISEL trial were also required to be intolerant of or have progressed within 90 days following their most recent chemotherapy regimen. At the same time, the proportion of patients in the ISEL trial with progressive disease as the best response to previous chemotherapy was high, at approximately 39%, compared to only 28% for BR.21. As a result, the ISEL population comprised a poorer prognostic group, which might benefit to a lesser degree from therapy. Another possible explanation is that the dosing of gefitinib used in the ISEL trial was inadequate. In ISEL, gefitinib was administered at 250 mg/day, substantially below the maximum tolerated dose of 800 mg/day established in phase I testing (64), whereas erlotinib was given at 150 mg/day in BR.21, close to its maximum tolerated dose of 200 mg/day (65). However, the results of the IDEAL 1 and 2 trials would argue against that explanation, given the similarity in RR and survival endpoints for gefitinib at 250 mg/day and 500 mg/day.

Exploratory analyses have suggested that some patient subgroups may be more likely to benefit from therapy with an EGFR-I. Female gender, adenocarcinoma histology and a history of never smoking were associated with a higher RR to erlotinib (40), and female gender and adenocarcinoma histology predicted response to gefitinib (18,19). Of those, smoking history was the only factor that predicted for a differential *survival* benefit for erlotinib (40,57), whereas both smoking history and Asian ethnicity predicted *survival* benefit with gefitinib (41). Molecular analyses have indicated that EGFR expression, but not EGFR mutation, was a predictor of response to erlotinib (40,57), whereas EGFR mutation was associated with a higher RR for gefitinib (59). However, none of the molecular markers analyzed were predictive of survival benefit for either agent. Therefore, at the present time there is no validated set of clinical or molecular markers on which to base selection of patients for treatment with an EGFR-I.

A small molecule receptor tyrosine kinase inhibitor targeting both the vascular endothelial growth factor receptor-2 (VEGFR-2) and EGFR, designated ZD6474 (Zactima®), has been evaluated as second-line therapy for NSCLC in two randomized phase II trials, as a single agent compared to docetaxel (66), and in combination with docetaxel compared to docetaxel alone (67,68). Both trials have been published in abstract form only but did not meet criteria for inclusion in this systematic review because pre-specified outcomes of interest were not reported. Progression-free survival, which was the primary endpoint for both trials, was shown to be superior for ZD6474 versus docetaxel and for the combination of ZD6474 plus docetaxel versus docetaxel alone. However, survival, RR, QOL and toxicity data have yet to be reported in detail. This agent is about to enter phase III testing in combination with docetaxel compared to docetaxel alone.

A number of other novel agents, including histone deacetylase inhibitors and the proteasome inhibitor bortezomib, have undergone preliminary testing in the treatment of relapsed/progressive NSCLC. Combination regimens incorporating the histone deacetylase inhibitors CI-994 and pivaloyloxymethyl butyrate plus chemotherapy have not been found superior to chemotherapy alone and will likely not go forward to phase III testing. In

contrast, bortezomib has shown promise, both as a single agent, and in combination with docetaxel (47,48).

Although there is no proven advantage for a specific order of second-line and subsequent therapies, the results of TAX 317 and BR.21 trials are generally supportive of a sequence in which docetaxel is followed by erlotinib. The TAX 317 trial included patients eligible for second and third line chemotherapy; however, three-quarters were treated in second line. BR.21 included patients that were considered not to be suitable candidates for second-line chemotherapy, as well as patients receiving second-line and subsequent-line therapy. Approximately one-half were treated in third line. In addition, patients enrolled in BR.21 were allowed to receive docetaxel as second-line therapy, whereas TAX 317 was conducted at a time when erlotinib was not available for second-line use. Finally, there is a substantial and consistent body of phase III data that supports the efficacy of docetaxel as second-line therapy, while only a single phase III trial supports the benefit of erlotinib. No phase III randomized trial has yet been completed that has compared docetaxel directly with an EGFR-I as second-line therapy, although accrual to two such studies is ongoing (see the *Ongoing Trials* section of this review). In the SIGN randomized phase II trial, which evaluated gefitinib alongside docetaxel as second-line therapy, MS was similar for both treatments, and within the range anticipated (MS of 7.5 months for gefitinib and 7.1 months for docetaxel). However, that trial was not designed to compare survival outcomes, and was underpowered to test non-inferiority.

ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database on the Internet (http://cancernet.nci.nih.gov/trialsrch.shtml) was searched for ongoing trials. The ongoing trials of second-line or subsequent systemic therapy in NSCLC are summarized in Appendix D. In addition, several of the trials included in this paper have to date been reported in abstract or presentation only. Those trials may still be ongoing, and the published results should be considered preliminary.

CONFLICT OF INTEREST

None of the authors of this systematic review declared any conflicts of interest.

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For a complete list of the Lung DSG members, please visit the Cancer Care Ontario web site at: http://www.cancercare.on.ca/

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Appendix A. Table of literature search terms used for electronic databases[a]

Search Categories		Database and Search Dates		
		MEDLINE	**EMBASE**	**Cochrane Library**
		1966-2005 (November)	1980-2005 (week 53)	2005, Issue 4
Disease	Index terms	Carcinoma, non-small-cell lung; Lung adenocarcinoma; Lung alveolus cell carcinoma; Lung cancer; Lung carcinogenesis; Lung non small cell cancer; Lung squamous cell carcinoma.		
	Text words	Non-small cell lung		
Intervention	Index terms	Antineoplastic agent(s); antineoplastic protocols; antineoplastic combined chemotherapy protocols; Drug therapy combinations; Systemic therapy, Cancer chemotherapy; Drug therapy.		
	Text words	Chemotherapy		
Study Design	Index terms	Double-blind method; Double-blind procedure; Phase 2 clinical trial; Phase 3 clinical trial; Random allocation; Randomized controlled trial(s); Single-blind method; Single-blind procedure; Meta analysis; Practice guideline; Methodology; Cohort Analysis; Controlled clinical trial; Major clinical study		
	Text words	Randomized controlled trial; Practice Guideline; Meta-Analysis; Systematic Overview/review; Quantitative overview/review; Data pool		
Disease Stage	Index terms	Recurrence, Neoplasm recurrence, local; Salvage therapy; Retreatment; Cancer recurrence; Recurrent cancer; Recurrent disease; Tumor recurrence; Relapse		
	Text words	Previous treatment; Prior treatment; Previous chemotherapy; Prior chemotherapy; Relapse, Salvage; Refract; Rechallenge; Retreat; Reinduct; Recurrence; Second line, Third line; Fourth line;		
Limits		English language		

[a] Some search terms were specific to an individual database.

Appendix B. Ineligible randomized trials (< 50 patients per treatment arm).

Reference	N	Treatment arms	Response Rate % (CR + PR)	Survival Median, Months
Marangolo 2000 (69) [a]	14	Docetaxel 100 mg/m^2 q3wks x 6	12.5	NR
	11	Vinorelbine 30 mg/m^2 days 1 and 8, q3wks x 6	0	
Takenaka 2001 (70) [a]	10	Docetaxel 60 mg/m^2 q3wks	20	NR
	15	Carboplatin AUC 2 + irinotecan 50 mg/m^2 days 1, 8 and 15, q4wks	0	
Talbot 2002 (71) [a]	44 total	E7070 700 mg/m^2 q3wks	6	NR
		E7070 130 mg/m^2 daily for 5 days, q3wks	0	
Cortas 2003 (60) [a]	19	Rebeccamycin analogue 500 mg/m^2 q3wks x 6	5	10
	17	Rebeccamycin analogue 140 mg/m^2 daily for 5 days, q3wks x 6	0	14
Esteban 2003 (72)	35	Docetaxel 36 mg/m^2 wkly for 6wks, repeated q8wks	3	6.0
	36	Paclitaxel 80 mg/m^2 (1-hour infusion) wkly for 6wks, repeated q8wks	14	3.5
Tsai 2003 (73) [a c]	43 total	Docetaxel 66 mg/m^2 q3wks	13.6	7.7
		Docetaxel 33 mg/m^2 wkly for 2wks, repeated q3wks	28.6	6.4
Chen 2004 (74,75) [a d]	26 [b]	Docetaxel 75 mg/m^2 q3wks	3.8	7.6
	43 [b]	Docetaxel 40 mg/m^2 wkly for 2wks, repeated q3wks	9.3	5.3
	46 [b]	Docetaxel 35 mg/m^2 wkly for 3wks, repeated q4wks	21.7	7.0
Ross 2004 (62) [a]	62 total	Docetaxel 35 mg/m^2 wkly for 6wks	NR	5.9
		Docetaxel 35 mg/m^2 + CBR96-doxorubicin immunoconjugate 200-350 mg/m^2 wkly for 6wks, repeated q8wks		7.3
Dawood 2005 (76) [a c]	22 total	Docetaxel 36 mg/m^2 wkly 3 out of 4 wks x 6	NR	18.2 [e]
		Docetaxel 75 mg/m^2 q3wks x 6		17.9 [e]
Robinet 2005 (77) [a]	29	Docetaxel 75 mg/m^2 q3wks	10	NR
	31	Docetaxel 75 mg/m^2 q3wks + gefitinib 250 mg/daily	19	

Abbreviations: AUC = area under the curve, CR = complete response, N = number of patients, NR = not reported, PR = partial response, q = every, wk(s) = week(s).
[a] Abstract
[b] Total number of patients randomized was 126
[c] The results from these trials were not included in the meta analysis as the abstract did not provide six-month survival rates, or a survival curve and toxicity data was incompletely reported
[d] The results from this trial were not included in the meta analysis as the data were preliminary and the trial may not have finished patient accrual
[e] Mean overall survival

Appendix C: Trial treatment regimens.

Reference	Treatment dose/schedule
Single-agent docetaxel compared with BSC or another single agent	
Shepherd 2000 (16) (TAX 317)	1. Docetaxel 100 mg/m^2 q3wks (during first half of study) 2. Docetaxel 75 mg/m^2 q3wks (during second half of study) 3. Best supportive care determined by treating physician
Fossella 2000 (17) (TAX 320)	1. Docetaxel 100 mg/m^2 q3wks (during first half of study) 2. Docetaxel 75 mg/m^2 q3wks (during second half of study) 3. Vinorelbine 30 mg/m^2 days 1, 8 and 15, q3wks OR ifosfamide 2 mg/m^2 days 1-3, q3wks Choice of vinorelbine or ifosfamide at investigator's discretion
Hanna 2004 (21)	1. Docetaxel 75 mg/m^2 q3wks 2. Pemetrexed 500 mg/m^2 q3wks + 350-1,000 µg oral folic acid daily + 1,000 µg intramuscular vitamin B12 q9wks, starting 1-2 wks before the 1st dose of pemetrexed and ending after the last dose of pemetrexed (3wks after last dose for folic acid)
Ramlau 2005 (23,24)	1. Docetaxel 75 mg/m^2 q3wks x 4 (or until disease progression) 2. Oral topotecan 2.3mg/m^2 days 1-5 q3 wks x 4 (or until disease progression)
Single-agent docetaxel dose or schedule comparisons	
Camps 2003 (25,26)	1. Docetaxel 75 mg/m^2 q3wks 2. Docetaxel 36 mg/m^2 wkly for 6wks, repeated q8wks
Gridelli 2004 (27)	1. Docetaxel 75 mg/m^2 q3wks x 6 2. Docetaxel 33.3 mg/m^2 wkly for 6wks, repeated q8wks x 2
Schuette 2005 (28)	1. Docetaxel 75 mg/m^2 q3wks x 6 2. Docetaxel 35 mg/m^2 wkly for 3wks, repeated q4wks x 6
Gervais 2005 (29)	1. Docetaxel 75 mg/m^2 q3wks x 6 2. Docetaxel 40 mg/m^2 wkly for 6wks, repeated q8wks x 2
Quoix 2004 (30)	1. Docetaxel 75 mg/m^2 q3wks x 6 2. Docetaxel 100 mg/m^2 q3wks x 6
Docetaxel-based combination chemotherapy comparisons	
Takeda 2004 (31,32)	1. Docetaxel 60 mg/m^2 q3wks x 4 2. Docetaxel 60 mg/m^2 day 8 + gemcitabine 800 mg/m^2 days 1 and 8, q3wks x 4
Pectasides 2005 (33)	1. Docetaxel 75 mg/m^2 q3wks 2. Docetaxel 30 mg/m^2 + irinotecan 60 mg/m^2, days 1 and 8, q3wks
Wachters 2005 (34)	1. Docetaxel 75 mg/m^2 q3wks x 5 2. Docetaxel 60 mg/m^2 + irinotecan 200 mg/m^2, both on day 1, + lenogastrim 150 µg/m^2, days 2-12, q3wks x 5
Lilenbaum 2005 (37)	1. Docetaxel 35 mg/m^2 day 1 + irinotecan 60 mg/m^2, days 1 and 8, q3wks 2. As above + celecoxib 400 mg BID, starting day 1. 3 Gemcitabine 1,000 mg/m^2 day 1 + irinotecan 100 mg/m^2, days 1 and 8, q3wks 4. As above + celecoxib 400 mg BID, starting day 1.
Combination chemotherapy comparisons without docetaxel	
Georgoulias 2004 (38)	1. Irinotecan 300 mg/m^2 q3wks 2. Gemcitabine 1,000 mg/m^2 days 1 and 8 + irinotecan 300 mg/m^2 day 8, q3wks
Georgoulias 2005 (39)	1. Cisplatin 80 mg/m^2 day 1 q3wks 2. Cisplatin 80 mg/m^2 day 8 + irinotecan 110 mg/m^2 or 100 mg/m^2 days 1 and 8, q3wks
Other systemic therapy comparisons - EGFR inhibitors	
Shepherd 2005 (40)	1. Erlotinib 150 mg/day 2. Placebo daily
Thatcher 2005 (41) (ISEL)	1. Gefitinib 250 mg/day 2. Placebo daily
Fukuoka 2003 (18) (IDEAL 1)	1. Gefitinib 250 mg/day 2. Gefitinib 500 mg/day
Kris 2003 (19) (IDEAL 2)	1. Gefitinib 250 mg/day 2. Gefitinib 500 mg/day
Cufer 2005 (42,43)	1. Docetaxel 75 mg/m^2 q3wks 2. Oral Gefitinib 250 mg/day

Other systemic therapy agents	
Von Pawel 2002 (44)	1. Gemcitabine 1,000 mg/m^2 days 1, 8, and 15 + placebo days 1-21, q4wks 2. Gemcitabine 1,000 mg/m^2 days 1, 8, and 15 + CI-994 6 mg/m^2 days 1-21, q4wks
Raghunadharao 2005 (46)	1. Pivanex 2.5 g/m^2 days 1-3 + docetaxel 75 mg/m^2 day 4, q3wks 2. Docetaxel 75 mg/m^2 day 1 q3wks
Fanucchi 2005 (47,48)	1. Bortezomib 1.5 mg/m^2 days 1, 4, 8 and 11, q3wks 2. Docetaxel 75 mg/m^2 day 1 (1-hour infusion) + bortezomib 1.3 mg/m^2 days 1 (1 hour after docetaxel), 4, 8 and 11, q3wks
Other systemic therapy agents dose / schedule comparisons	
Vansteenkiste 2003 (49,50)	1. BMS-247550 50 mg/m^2 (1-hour infusion) q3wks, later reduced to 40 mg/m^2 (3-hour infusion) and then 32 mg/m^2 (3-hour infusion) because of toxicity 2. BMS-247550 6 mg/m^2 (1-hour infusion) daily for 5 days, q3wks

Abbreviations: AUC = area under the curve, BSC = best supportive care, EGFR = epidermal growth factor receptor, q = every, wk(s) = week(s).

Appendix D. Ongoing randomized phase II or III trials of second-line or subsequent systemic therapy in NSCLC [a]

Protocol IDs	Title and details of trial
1839IL/0721 NCT00076388 (INTEREST)	Phase III Randomized Trial Comparing Gefitinib Versus Docetaxel in Patients With Recurrent or Progressive NSCLC
104864/615 NCT00065182	Combination Chemotherapy Treatment For Advanced NSCLC Patients Having Prior Chemotherapy
CP02-0452 NCT00095199	Phase III Randomized Study of Docetaxel or Pemetrexed With or Without Cetuximab in Patients With Recurrent or Progressive Non-Small Cell Lung Cancer
PROGEN-PR88202 AUS-RNSH-0309-183M, NCT00103389	Phase II Randomized Study of Docetaxel With Versus Without PI-88 in Patients With Stage IIIB or IV NSCLC
OSI13364g, NCT00130728	Phase III Randomized Study of Bevacizumab in Combination With Tarceva for Advanced NSCLC
PRA-OSI2950g GENENTECH-OSI2950g, UCLA-0408116-01, NCT00098410	Phase II Randomized Study of Bevacizumab Combined With Either Docetaxel, Pemetrexed, or Erlotinib Versus Docetaxel or Pemetrexed Alone in Patients With Recurrent or Refractory Stage IIIB or IV NSCLC
8433, NCT00078260	Phase III Randomized Study of Pemetrexed in Patients with NSCLC Who Have Failed Prior Platinum-containing Chemotherapy
MSKCC-03090, ZENECA-6474IL/0003, NCT00072423 (66)	Phase II Randomized Study of ZD6474 Versus Gefitinib in Patients With Stage IIIB/IV NSCLC Who Failed Prior First-line Platinum-based Chemotherapy (CLOSED, final results to be reported)
UCLA-0208009, ZENECA-6474IL/0006, NCT00054093 (67,68)	Phase II Randomized Study of ZD6474 And Docetaxel in Patients With Locally-advanced or Metastatic NSCLC Refractory to Platinum-based Chemotherapy (CLOSED, final results to be reported)
VA 15-32	Phase III Randomized Study Comparing Gefitinib Versus Docetaxel as Second-line Therapy for NSCLC.
CTI-PGT302, CWRU-CTI-1503, NCT00054184 (STELLAR 2)	Phase III Randomized Study of Polyglutamate Paclitaxel (CT-2103) Versus Docetaxel as Second-line Therapy in Patients With Progressive NSCLC (CLOSED, final results to be reported)

[a] Reported in the National Cancer Institute (NCI) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and accessed November 2005.

Appendix E: Quality of life instruments used in lung cancer trials

Scale	No. of Items	Categories/Domains	Time Frame
General Quality of Life Measures			
EORTC QLQ-C30 (78,79)	30	*Functional subscales:* physical, role, cognitive, emotional, social and global QOL *Symptom subscales:* fatigue, pain, nausea/vomiting *Single-item symptoms:* dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact	Past Week
Euro QOL (80)	15	Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression Overall Health status	Present
Daily Diary Card (81)	NR	Rapid and transient changes of sleeping, mood, well-being, level of activity, nausea/vomit, appetite loss and pain	Present
Lung Cancer Specific Quality of Life Measures			
EORTC QLQ -LC13 (78,82)	13	Dyspnea Subscale *10 symptom items*: cough, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, shoulder pain, other pain and pain medication	Past Week
LCSS (78,83,84)	9 6	*Six symptoms*: appetite, fatigue, cough, dyspnea, hemoptysis, and pain *3 global items:* Symptomatic distress, activity status, overall QOL *Optional Observer scale*: appetite, fatigue, cough, dyspnoea, haemoptysis, pain	Past Day
FACT (85) FACT – L (86) FACT – T (87)	27 9 16	*General*: Physical, social/family, emotional, and functional well-being; and relationship with doctor *Lung Cancer Subscale*: symptoms (shortness of breath, loss of weight, tightness in chest, coughing) cognitive function *Taxane Subscale*: Neurotoxicity and Symptoms (arthralgia, myalgia, and skin discoloration)	Past Week

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer Module, LCSS: Lung Cancer Symptom Scale, FACT-L: Functional Assessment of Cancer Therapy – Lung, FACT-T: Functional Assessment of Cancer Therapy – Taxane

Evidence-based Series 7-19: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer: Guideline Development and External Review – Methods and Results

J. Noble, P. Ellis, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group

The 2006 guideline recommendations require an

UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2005 and 2012.

Report Date: March 27, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review*. This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results*. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This Evidence-based Series was developed by the Lung Cancer DSG of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the use of second-line or subsequent systemic therapy in the treatment of recurrent or progressive NSCLC, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel were regarding the level of evidence included in the guideline, specifically the inclusion of randomized phase II trials and the section on novel agents. The Panel noted that the level of evidence supporting the recommendation for gefitinib monotherapy as second-line or subsequent treatment was limited. The Panel also suggested that the reporting of response rates be deleted and the reporting of results of randomized phase II trials be non-comparative. The Lung DSG agreed that the study selection criteria were too broadly defined. Trials with less than 50 patients per treatment arm were excluded from the guideline and placed in an appendix. Randomized phase II trials were retained for questions for which there was not randomized phase III evidence available and were included in the meta-analyses conducted for dose/scheduling of docetaxel. The section on novel agents was condensed, and in future guidelines, the Lung DSG will consider excluding novel agents. The Lung DSG explicitly acknowledged the limitations of the evidence for gefitinib recommendation by clarifying the evidence for this recommendation. Response rate data was retained in the guideline as clinical practice relies on the assessment of response as an indication to continue treatment. Text in the *Results* section that compared outcomes between randomized groups of non-comparative phase II trials was revised to be non-comparative. Editorial changes were also made as suggested by the Panel.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel, the Lung DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review January 31, 2006)

Target Population

These recommendations apply to adult patients with advanced or metastatic NSCLC that has recurred or progressed following prior systemic therapy.

Recommendations and Key Evidence

- **Single-agent docetaxel (Taxotere®) at a dose of 75 mg/m^2 every three weeks is recommended as second-line therapy for patients with recurrent or progressive NSCLC and adequate performance status (0-2).**

  There is evidence from two randomized phase III trials of a significant benefit in overall survival and QOL for single-agent docetaxel when used as second-line therapy for recurrent or progressive NSCLC. In one trial, comparing docetaxel at 75 mg/m^2 to BSC, median survival was increased from 4.6 months to 7.5 months (p=0.01 log rank), and one-year survival from 12% to 37% (p=0.003 chi-square). Treatment with docetaxel was also associated with a significant improvement in patient-related pain compared to BSC (p=0.005). In a second trial, comparing docetaxel with vinorelbine or ifosfamide, median survival was not significantly different, but one-year survival was superior for docetaxel at 75 mg/m^2 (32% versus 19%, p=0.025, chi-square). Although the optimal duration of therapy is unknown, in both trials, treatment with docetaxel was continued until disease progression or development of unacceptable toxicity.

- **Single-agent pemetrexed (Alimta®) at a dose of 500 mg/m^2 every three weeks is also an option for second-line therapy of recurrent or progressive disease, if available. This chemotherapy should be administered with vitamin supplements: oral folic acid 350-1,000 mcg daily and intramuscular vitamin B_{12} 1,000 mcg every nine weeks, beginning between one to two weeks before, and continuing until three weeks after chemotherapy.**

  The results of a single randomized phase III trial suggest a similar survival benefit for single-agent pemetrexed at 500 mg/m^2, combined with vitamin supplementation, compared to docetaxel at 75 mg/m^2, when used as second-line therapy. Median survival was 8.3 months for pemetrexed versus 7.9 months for docetaxel, with one-year survival of 29.7% for both treatments. A test for non-inferiority using the percent retention method, indicated that pemetrexed retained >50% of the survival benefit of docetaxel over BSC (p=0.047). However, the primary test of non-inferiority, which required that survival for pemetrexed be ≤ 10% worse than docetaxel, was not statistically significant (p=0.226). Hematologic toxicities, including febrile neutropenia, occurred with significantly lower frequency with pemetrexed than with docetaxel. A comparison of QOL measures showed no significant difference between the two treatments.

- **Oral topotecan at a dose of 2.3 mg/m^2 administered day 1-5 every three weeks is not recommended for second-line therapy of recurrent or progressive disease.**

  The results of a single randomized phase III trial suggest a similar one-year survival rate for oral topotecan at a dose of 2.3 mg/m^2 compared to docetaxel at 75 mg/m^2, when used as second-line therapy. The one-year survival was 25.1% for topotecan versus 28.7% for docetaxel; however, the overall survival difference approached statistical significance in favour of docetaxel (hazard ratio, 1.16; 95% confidence interval, 1.00-1.35; p=0.057), with a median survival of 27.9 weeks and 30.7 weeks for topotecan and docetaxel, respectively. A comparison of QOL measures also significantly favoured docetaxel.

- **Docetaxel administered at a dose of 33.3-40 mg/m^2 (for six weeks on an eight-week cycle or for three weeks on a four-week cycle) may be considered in patients at high risk of hematologic toxicity or with a previous history of febrile neutropenia using the three-weekly docetaxel schedule.**

  Evidence from four randomized trials suggests that docetaxel administered weekly at a dose of between 33.3 mg/m^2 and 40 mg/m^2 may achieve similar survival and superior tolerability to docetaxel administered three-weekly at a dose of 75 mg/m^2. A pooled analysis of six-month survival data from those trials provided a hazard ratio of 0.99 (95% confidence interval, 0.84-1.16, p=0.91). The benefit for the weekly regimen in terms of a reduction in the incidence of febrile neutropenia approached statistical significance (hazard ratio, 0.29; 95% confidence interval, 0.08-1.12, p=0.07). However, this potential advantage must be weighed against the greater inconvenience to the patient of weekly treatment.

- **Combination chemotherapy (docetaxel-based or other) is not currently recommended as second-line or subsequent therapy for recurrent or progressive disease.**

  Docetaxel-based and other combination chemotherapy regimens have yet to be compared to single-agent docetaxel in a fully published randomized phase III trial. The results of several small trials suggest promising activity for some combination regimens, but those regimens will require further testing.

- **Erlotinib at a dose of 150 mg/day is recommended as third-line therapy for patients with advanced recurrent or progressive NSCLC who maintain a good performance status following previous platinum-based and docetaxel (or pemetrexed) chemotherapy. Erlotinib is also an option for second-line therapy, particularly in patients who are not candidates for chemotherapy or for those with progression after first-line docetaxel-platinum chemotherapy.**

  There is evidence from a single randomized phase III trial of a significant benefit in overall survival and QOL for the epidermal growth factor receptor inhibitor (EGFRI) erlotinib (Tarceva®) when compared to placebo as second or third-line systemic therapy. Median survival was increased from 4.7 months to 6.7 months ($p<0.001$ log rank), and one-year survival from 22% to 31%. Erlotinib was also associated with a significant delay in time to deterioration for cough ($p=0.04$), dyspnea ($p=0.03$) and pain ($p=0.04$), and an improvement in overall physical QOL ($p=0.01$), compared to placebo.

- **Gefitinib at a dose of 250 mg/day may be considered for second-line and subsequent therapy only for selected symptomatic patients who are not candidates for chemotherapy and for whom erlotinib is not available.**

  The results of a single randomized phase III trial revealed no statistically significant survival or QOL benefit for the EGFRI gefitinib (Iressa®) when compared to placebo as second-line or subsequent therapy. Gefitinib was associated with a superior tumour response rate (8% vs 1%, $p<0.0001$) and symptom improvement. Two randomized phase II trials suggest that modest tumour response rates and symptom control can be achieved with gefitinib. Although a significant survival benefit has not been demonstrated for this agent in a placebo-controlled study, the trials suggest that gefitinib may provide clinically important symptomatic benefits

Methods

Feedback was obtained through a mailed survey of 129 practitioners in Ontario, including 33 medical oncologists, 32 respirologists, 25 surgeons, 21 radiation oncologists, and 18 other practitioners. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on January 31, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Sixty responses were received out of the 129 surveys sent (47% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 30 indicated that the report was relevant to their clinical practice, including medical oncologists (57%), surgeons (20%), and radiation oncologists (7%) and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 8.

Table 8. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	30 (100%)	0	0
There is a need for a guideline on this topic.	28 (93%)	2 (7%)	0
The literature search is relevant and complete.	29 (97%)	1 (3%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	27 (90%)	3 (10%)	0
The draft recommendations in the report are clear.	27 (90%)	2 (7%)	1 (3%)
I agree with the draft recommendations as stated.	27 (90%)	3 (10%)	0
This report should be approved as a practice guideline.	27 (90%)	2 (7%)	1 (3%)

If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? [a]	Very likely or likely	Unsure	Not at all likely or unlikely
	23 (79%)	4 (14%)	2 (7%)

[a] One respondent did not answer the question

Summary of Written Comments

Eight respondents (27%) provided written comments, most of which indicated their support for the summary of the evidence and the final recommendations. There were three issues raised that required a response by the DSG.

1. Two practitioners expressed concerns regarding the costs of erlotinib and that it is not currently funded in Ontario.
2. One practitioner stated that they would very rarely offer third-line chemotherapy to any patient with NSCLC.
3. One practitioner questioned the recommendation for gefitinib as the ISEL trial included a refractory population and did not find a survival benefit. The practitioner also commented that if erlotinib is recommended, there should be access for all patients in Ontario.

Modifications/Actions

The DSG responses to the above comments are summarized below.

1. Although erlotinib is not currently funded in Ontario, the Lung DSG submitted a draft of this Evidence-Based Series to the Drug Quality and Therapeutics Committee -Special Oncology Subcommittee (DQTC-SOS) of Ontario in 2005 for funding consideration of erlotinib. The fiscal issues of erlotinib are beyond the scope of this guideline.
2. The Lung DSG supports the recommendation for third-line therapy as there is evidence of significant benefit in survival and quality of life as compared to placebo. As always, the patient and physician should have a full discussion of the benefits, limitations, and toxicities of therapy.
3. The Lung DSG acknowledges that the evidence is stronger for erlotinib than gefitinib and that all patients should have access to erlotinib. The recommendation for gefitinib was maintained as although a significant survival benefit was not demonstrated for gefitinib in a placebo-controlled study, modest tumour response rates and symptom control have been achieved with gefitinib. Also since resources are limited, if there is not access to erlotinib, the Lung DSG recommends that gefitinib be considered, as it may provide clinically important symptomatic benefits.

Policy Review

A draft of this evidence-based series was sent for review by the DQTC-SOS of Ontario in 2005 for funding consideration of erlotinib for advanced non-small cell lung cancer patients who have failed prior chemotherapy.

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Evidence-based Series 7-19: Section 4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer

Guideline Review Summary

Review Date: October 1, 2012

The 2006 guideline recommendations require an

UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making

OVERVIEW

The original version of this guidance document was released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario, in 2006. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations require an update. On October 1, 2012, the Lung Cancer Disease Site Group (DSG) agreed to update the recommendations found in Section 1 (Clinical Practice Guideline).

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What are the survival and/or quality of life (QOL) benefits of systemic therapy compared with best supportive care (BSC) in the second-line and subsequent treatment of recurrent or progressive non-small cell lung cancer (NSCLC)?
2. Which systemic therapy agent or combination of agents provide the greatest improvement in survival and/or QOL in the second-line and subsequent treatment of recurrent or progressive disease?
3. What are the optimal doses and schedules of different systemic therapy agents in the second-line or subsequent treatment of recurrent or progressive disease?

Literature Search and New Evidence

The new search (December 2005 to August 2012) yielded 57 references representing nine meta-analysis (one meta-analysis had two publications), one pooled analysis, and 37 RCTs (two RCTs had two publications each, two RCTs had three publications each, and one RCT had four publications), found evaluating the role of second-line or subsequent systemic therapy in the management of recurrent or

progressive non-small cell lung cancer. Twenty of these RCTs are already included in the meta-analysis and pooled analysis, while 17 references are potentially new studies. Twelve of these new studies had full text publications and five were in abstract form. There were two ongoing studies identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data does not contradict existing recommendations. However, there needs to be some modifications to the current recommendations due to the large volume of evidence available. Hence, the Lung Cancer DSG decided that the 2006 recommendations on second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer require an UPDATE.

Document Summary and Review Tool

Number and title of document under review	7-19 Second-line or Subsequent Systemic Therapy for Recurrent or Progressive Non-Small Cell Lung Cancer
Current Report Date	March 27, 2006
Clinical Expert	Dr. Peter Ellis
Research Coordinator	Nofisat Ismaila
Date Assessed	September 2011
Approval Date and Review Outcome (once completed)	Oct 1, 2012 (UPDATE)

Original Question(s):

4. What are the survival and/or quality of life (QOL) benefits of systemic therapy compared with best supportive care (BSC) in the second-line and subsequent treatment of recurrent or progressive non-small cell lung cancer (NSCLC)?
5. Which systemic therapy agent or combination of agents provide the greatest improvement in survival and/or QOL in the second-line and subsequent treatment of recurrent or progressive disease?
6. What are the optimal doses and schedules of different systemic therapy agents in the second-line or subsequent treatment of recurrent or progressive disease?

Tumour response rate, symptom control, and toxicity were secondary outcomes of interest.

Target Population:

Adult patients with advanced or metastatic NSCLC that has recurred or progressed following prior systemic therapy.

Study Section Criteria:

Inclusion criteria

Articles published as full reports or as abstracts were selected for inclusion if they focused on second-line or subsequent systemic therapy for recurrent or progressive NSCLC, reported outcomes of interest, and were:

1. Systematic reviews or practice guidelines of systemic therapy; or
2. Meta-analyses comparing systemic therapy with BSC or another systemic therapy; or
3. Randomized trials comparing different systemic therapy agents or regimens, or systemic therapy with BSC; or
4. Randomized trials comparing different doses and/or schedules of systemic therapy agents.

Exclusion criteria

1. Systematic reviews or meta-analyses that pre-dated, or confined their analysis to, trials included in the 2001 practice guideline developed by the Lung DSG on the role of single-agent docetaxel as second-line treatment for advanced NSCLC.
2. Trials that included a mix of untreated and previously treated patients.
3. Articles published in a language other than English.
4. Trials that included less than 50 patients per trial arm. Trials with less than 100 patients were considered underpowered to detect any clinically meaningful difference in effect given the range of typical accrual times, follow up times, and times-to-event. Trials with less than 50 patients per trial arm are reported in Appendix B and are included in any relevant meta-analyses conducted.

Search Details:

- December 2005 to August 2012 (Medline May wk 2 + Embase week 21)
- December 2005 to August 2012 (ASCO Annual Meeting)
- December 2005 to August 2012 (Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 1195 total hits from Medline, Embase + 63 total hits from ASCO + 19 total hits from clinicaltrials.gov, 57 references representing 9 meta-analysis (I meta-analysis had 2 publications), 1 pooled analysis, and 37 RCTs (2 RCT had 2 publications each, 2 RCTs had 3 publications each and 1 RCT had 4 publications), were found evaluating the role of second-line or subsequent systemic therapy in the management of recurrent or progressive non-small cell lung cancer. Twenty of these RCTs are already included in the meta-analysis and pooled analysis, while 17 references are potentially new studies. Twelve of these new studies had full text publications and 5 were in abstract form. There were 2 ongoing studies identified from clinicaltrials.gov.

Meta-analysis					
Interventions	**Population**	**N of studies**	**Outcomes**	**Brief results**	**References**
Pemetrexed-based doublet Vs. Single-agent pemetrexed	Patients pathologically confirmed of NSCLC and previously treated (N=1,186)	5 RCTs	**P**: OS **S**: PFS, ORR and Toxicity	• There was significant improvement in PFS (HR 0.82, 95% CI 0.71–0.95, P = 0.007) and overall response rate (OR 2.39, 95% CI 1.58–3.62, P = 0.000) in pemetrexed-based doublet group, compared with pemetrexed alone, though the pooled HR for overall survival (HR 0.89, 95% CI 0.76–1.04; P = 0.129) showed no significant difference between the two groups. • There were more incidences of grade 3 or 4 neutropenia (OR 2.3, 95% CI 1.4-3.77, P = 0.001), thrombocytopenia (OR 6.41, 95% CI 2.57–16.0, P = 0.000), and leucopenia (OR 2.45, 95% CI 1.13–5.34, P = 0.024) in pemetrexed-based doublet group. • With regard to the risk of grade 3 or 4 anemia (OR 0.71, 95% CI 0.17- 2.91, P = 0.629) and fatigue (OR 1.47, 95% CI 0.92–2.35, P = 0.104), there was no significant difference between the two groups.	Qi et al 2012
Docetaxel-based doublet Vs. Single-agent docetaxel	Patients pathologically confirmed of NSCLC and previously treated (N=2,126)	8 RCTs	**P**: OS **S**: PFS, ORR, 1 yr survival rate and Toxicity	• There was significant improvement in PFS (HR 0.81, 95% CI 0.69–0.96, P = 0.013) and overall response rate (OR 1.42, 95% CI 1.13–1.80, P = 0.03) in docetaxel-based doublet group, compared with docetaxel alone, though the pooled HR for overall survival (HR 0.93, 95% CI 0.80–1.07, P = 0.308) showed no significant difference between the two groups. • There were more incidences of grade 3 or 4 neutropenia (OR 1.2, 95% CI 1.00-1.45, P = 0.05), thrombocytopenia (OR 4.53, 95% CI 1.75–11.75, P = 0.002), and diarrhea (OR 1.78, 95% CI 1.16-2.74, P = 0.008) in docetaxel-based doublet group. • With regard to the risk of grade 3 or 4 anemia (OR 1.95, 95% CI 0.62–6.17, P = 0.25), fatigue (OR 1.09, 95% CI0.75-1.59, P = 0.66), and nausea and vomiting (OR 1.75, 95% CI 0.78–3.91, P = 0.17), there was no significant difference between the two groups.	Qi et al 2012
Vandetanib Vs. Standard second-line treatment	Patients pathologically confirmed of NSCLC and previously treated (N=3,292)	4 RCTs	**P**: OS **S**: PFS, ORR, and Toxicity	• There was significant improvement in PFS, HR, 0.91; 95% CI, 0.83-1.00; P = 0.039) and overall response rate, RR 1.49; 95% CI, 1.04-2.14; P = 0.03) in therapy with vandetanib group	Qi et al 2011

				compared with standard second-line therapy group, although the pooled HR for overall survival (HR, 0.95; 95% CI, 0.88-1.03; P = 0.191) showed no significant difference between the two groups. • There were less incidences of grade 3 or 4 anemia (RR, 0.39; 95% CI, 0.22-0.67; P = 0.001) in therapy with vandetanib group. • With regard to the risk of grade 3 or 4 neutropenia (RR, 1.19; 95% CI, 1.0–1.43; P = 0.054), diarrhea (RR, 1.38;95% CI, 1.0-1.94; P = 0.059), nausea and vomiting (RR, 0.77; 95% CI, 0.48-1.26; P = 0.308), rash (RR, 2.83; 95% CI, 0.73-10.9; P = 0.131), cough (RR, 1.19; 95% CI, 1.0-1.43; P = 0.054), and fatigue (RR, 1.0; 95% CI, 0.747-1.35; P = 0.971), there was no significant difference between the two groups	
Vandetanib-based therapy Vs. Non-vandetanib therapy	Patients pathologically confirmed of NSCLC and previously treated (N=4,492)	7 RCTs	PFS, OS ORR and toxicity	• When compared with placebo, vandetanib yielded a clear benefit for ORR (odds ratio (OR) = 2.04; 95% CI, 1.60-2.61; P < 0.001), and a clinically and statistically significant 25% improvement in PFS (hazard ratio (HR) = 0.75; 95% CI, 0.66- 0.85; P < 0.001). • However, these benefits did not translate into a significant improvement in OS (HR = 0.95; 95% CI, 0.88-1.04; P = 0.291). • Subgroup analyses showed that vandetanib 100mg/d was associated with greater antitumor activity than 300mg/d when given in combination with chemotherapy. • The pooled results demonstrated no statistically significant difference between vandetanib and single-targeted agents in PFS, ORR or OS. • Vandetanib was associated with more frequent adverse events	Zhang et al 2011 & Zhou et al 2011 (abstract)
Gefitinib Vs. Docetaxel	Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC; Patients received at least one previous chemotherapy regimen (N=2,257)	4 RCTs	OS, PFS, Overall response, QOL and toxicity	• The pooled HRs showed no significant difference in OS and PFS between the two groups (HR = 1.02, 95% CI = 0.92 – 1.12, p = 0.70; HR = 0.97, 95% CI = 0.88 – 1.07, p = 0.57, respectively). • Gefitinib significantly improved overall response rate (RR= 1.58, 95% CI = 1.02 – 2.45, p = 0.04) and QOL (RR = 1.55, 95% CI = 1.27 – 1.88, p = 0.00 by Functional Assessment of Cancer Therapy-Lung and RR = 1.86, 95% CI = 1.43 – 2.42, p = 0.00 by Trial Outcome Index, respectively). • Gefitinib had fewer grade 3 or 4 neutropenia and fatigue (OR = 0.02, 95% CI = 0.01 – 0.03, p = 0.00; and OR = 0.47, 95% CI = 0.32 – 0.70, p = 0.00, respectively), but more grade 3 or 4 rash (OR = 2.87, 95% CI = 1.24 – 6.63, p = 0.01) than docetaxel. • The grade 3 or 4 nausea, vomiting and diarrhea and symptom improvement were comparable between the two drugs	Jiang et al 2011
Primary analysis Chemotherapy or EGFR Inhibitor + BSC	NSCLC patients with progression after a first-line chemotherapy for	3 RCTs	**P:** 1-yr survival rate (SR) of the primary	• A significant heterogeneity was documented in the primary analysis for 1-year SR with odd ratio [OR] = 0.763 (p = 0.029).	Tassinari et al 2009

Vs. BSC alone **Secondary analysis** Docetaxel every 3 wk Vs. Any other alternative treatment	advanced disease (N=2,627) (N=5,952)	11 RCTs	analysis **S:** 1-yr SR of the secondary analysis, RR, and TPP of primary and secondary analyses	• No heterogeneity was documented for RR in the primary analysis, with OR = 0.165 (p < 0.001). • A modest heterogeneity was documented in the secondary analysis for 1-year SR and RR, with • 1-year SR OR = 0.924 (p = 0.122) and RR OR = 1.069 (p = 0.643)	
Single agent Vs. Doublet chemotherapy	Previously treated patients with advanced NSCLC (N=847)	6 RCTs	**P:** OS **S**: PFS, Objective RR, and toxicity	• Median age was 61 years. Performance status was 0 or 1 in 90%; 80% of patients had received previous platin-based chemotherapy. • OS was not significantly different between arms (P = .32). Median OS was 37.3 and 34.7 weeks in the doublet and single-agent arms, respectively. Hazard ratio (HR) was 0.92 (95% CI, 0.79 to 1.08). • Response rate was 15.1% with doublet and 7.3% with single-agent (P = .0004). • Median progression-free survival was 14 weeks for doublet and 11.7 weeks for single agent (P = .0009; HR, 0.79; 95% CI, 0.68 to 0.91). • There was no significant heterogeneity among trials for the three efficacy outcomes. • Patients treated with doublet chemotherapy had significantly more grade 3 to 4 hematologic (41% v 25%; P = .0001) and grade 3 to 4 nonhematologic toxicity (28% v 22%; P = .034)	Di Maio et al 2009
Weekly docetaxel (wD) Vs. Standard docetaxel once every 3 weeks (3wD)	Previously treated patients with advanced NSCLC (N=865)	5 RCTs	**P:** OS **S**: RR and toxicity	• Median age was 62 years (range, 26 to 80 years). • Performance status was 0 in 23%, 1 in 58%, and 2 in 16% of patients. • 91% of the patients had received previous platinum, and 14% had received previous paclitaxel. • With 733 deaths recorded (85%), median survival was 27.4 weeks for patients treated with 3wD, and 26.1 weeks for patients treated with wD (P = .24, log-rank test). • There was no significant heterogeneity among the five trials. No relevant differential effect was detected in subgroup analyses. • Significantly less severe and febrile neutropenia was reported with wD (P<.00001 for both), whereas no significant differences were observed for anemia, thrombocytopenia, and nonhematologic toxicity.	Di Maio et al 2007
Weekly docetaxel (wD) Vs. Standard docetaxel once every 3 weeks (3wD)	Previously treated patients with advanced NSCLC (N=1,018)	6 RCTs	**P:** OS **S**: ORR and toxicity	• When considering only phase III RCTs, OS did not significantly differ between the two arms (RR 1.01, 95% CI 0.76, 1.42, p = 0.785) with no significant heterogeneity (p = 0.42). • Regarding activity, no significant differences in favour of weekly docetaxel were found, although a trend for 3-weekly schedule was observed (RR 0.81, 95% CI 0.47, 1.40, p = 0.485), with no significant heterogeneity (p = 0.27). • No differences were found in the overall population also considering the	Bria et al 2006

				phase II trials. • Regarding G3-4 neutropenia, a significant homogenous advantage in favour of weekly docetaxel was found, with an absolute benefit of 15–19%.	
Pooled analysis of 2 RCTS					
Interventions	**Population**	**Follow-up**	**Outcomes**	**Brief results**	**References**
Pemetrexed 500 mg/m^2 (Arm A) Vs. Pemetrexed 500 mg/m^2 + Carboplatin AUC5 (PC)(Arm B)	Histologic or cytologic proof of advanced (NSCLC), relapse > 3 months after platinum-based chemotherapy, Median age, 62 years (n=479)	NR	**P:** OS	• In the overall population, survival was not improved by the addition of C to P; the HR for death was 0.88 (95%CI: 0.71-1.07; p = 0.202; p for heterogeneity = 0.693). • Objective response rate was increased in the PC arm with an OR of 1.78 (95%CI: 1.01-3.12; p = 0.046; p for heterogeneity = 0.060). • A non-statistically significant increase in PFS favouring combined CT was observed with a HR of 0.85 (95%CI: 0.71-1.02; p = 0.082; p for heterogeneity = 0.019). • In the subgroup analyses, there was a statistically significant interaction between histological subtype and treatment: the addition of C to P in pts with squamous tumours led to a statistically significant improvement of PFS from 2 to 3.2 months (adjusted HR: 0.42; 95%CI 0.27-0.65; p of interaction test = 0.001) and of OS from 5.4 to 9 months (adjusted HR: 0.57; 95%CI 0.36-0.90; p of interaction test = 0.05)	Ardizzoni et al 2011(Abstract) (pooled analysis of Smit et al 2009 and Tiseo et al 2010)
Randomized control trials					
Trials comparing double agent chemotherapy					
Erlotinib + bevacizumab Vs. Erlotinib + placebo	Patients with cytologically or histologically confirmed advanced-stage NSCLC that was recurrent or refractory after standard first-line chemotherapy or chemoradiotherapy Mean age, 65yrs (n=636)	Median, 19 months	**P:** OS **S:** PFS, ORR, duration of ORR and toxicity	• OS did not differ between the 2 groups (hazard ratio [HR] 0·97, 95% CI 0·80–1·18, p=0·7583). • Median overall survival was 9·3 months (IQR 4·1–21·6) for patients in the bevacizumab group compared with 9·2 months (3·8–20·2) for controls. • PFS seemed to be longer in the bevacizumab group (3·4 months [1·4–8·4]) than in the control group (1·7 months [1·3–4·1]; HR 0·62, 95% CI 0·52–0·75) and ORR suggested some clinical activity of bevacizumab and erlotinib. However, these secondary endpoint differences were not significant • In the bevacizumab group, 130 (42%) of 313 patients with safety data had a serious adverse event, compared with 114 (36%) controls. There were 20 (6%) grade 5 adverse events, including two arterial thromboembolic events, in the bevacizumab group, and 14 (4%) in the control group.	Herbst et al 2011
Paclitaxel/carboplatin (PC) Vs.	Patients with cytologically or histologically confirmed advanced-stage NSCLC that was recurrent or refractory after standard	Median, 20.6 months (PC), 19.5 months (VC)	**P:** ORR **S:** OS, TTP and toxicity	• The ORR was 18.6% (95% confidence interval, 9.85%-27.49%; one complete and 13 partial responses) in the PC arm and 7.7% (95% confidence interval, 1.78%-13.61%;	Pallis et al 2011

Vinorelbine/ Carboplatin (VC)	first-line chemotherapy Median age, 65yrs (n=153)			one complete and five partial responses) in the VC arm (P = .056). • Median time to tumor progression was 3.5 months (range, 0.3 - 23.73 months) and 3.07 months (range, 0.37-18.5) in the PC and VC arm, respectively (P= .287). • Median overall survival was 7.83 months (range, 0.3-45.03 months) and 7.60months (range, 0.5-30.27 months) for PC and VC arms, respectively (Pvalue=.633). • Chemotherapy was well-tolerated and grade III/IV toxicities were relatively infrequent. No toxic deaths were observed	
Trials comparing single agent chemotherapy					
Paclitaxel poliglumex (PPX) Vs. Docetaxel	Patients with histologically or cytologically confirmed advanced NSCLC and had been treated with a single platinum-based systemic therapy Median age, 62 yrs (n=849)	NR	**P:** OS **S:** TTP, QOL and Toxicity	• Median survival (6.9 months in both arms, hazard ratio=1.09, P=0.257), 1-year survival (PPX=25%, docetaxel=29%, P=0.134), and time to progression (PPX=2 months, docetaxel=2.6 months, P=0.075) were similar between treatment arms. • PPX was associated with significantly less grade 3 or 4 neutropenia (P<0.001) and febrile neutropenia (P=0.006). Grade 3 or 4 neuropathy (P<0.001) was more common in the PPX arm. • Patients receiving PPX had less alopecia and did not receive routine premedications. • More patients discontinued due to adverse events in the PPX arm compared to the docetaxel arm (34 vs 16%, P<0.001). • There was no difference between the two treatment groups in the proportion of subjects achieving at least a 2-point increase in FACT-LCS score from baseline to cycle 3 (P=0.329)	Paz-Ares et al 2008
Trials with single agent dose/schedule comparison					
Standard pemetrexed (P500) Vs. High dose pemetrexed (P900)	Patients with stage III or IV NSCLC, whose disease had progressed following prior platinum-containing chemotherapy Median age, 62 yrs (n=588)	NR	**P:** OS **S:** PFS and toxicity	• Accrual was terminated with 588/600 patients enrolled because an interim analysis indicated a low probability of improved survival and numerically greater toxicity on the P900 arm. • No statistical difference was observed between the treatment arms (P500 versus P900) for median survival {6.7 versus 6.9 months, hazard ratio [HR] = 1.0132 [95% confidence interval (CI) 0.837–1.226]}, progression-free survival [2.6 versus 2.8 months, HR = 0.9681 (95% CI 0.817–1.147)], or best overall tumor response [7.1% versus	Cullen et al 2008

				4.3% (P = 0.1616)]. • The incidence of drug-related grade 3/4 toxicity was typically <5% on both treatment arms, but was numerically higher on the P900 arm for most toxicity categories.	
Bortezomib 1.5 mg/m^2 (arm A) Vs. Bortezomib 1.3 mg/m^2 + Docetaxel 75 mg/m^2(arm B)	Patients with histologically/cytologically confirmed inoperable, locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, who had received one prior chemotherapy regimen for locally advanced or metastatic disease Median age, 63 years (n=155)	NR	**P:** Tumor response rate **S:** TTP, OS, safety and tolerability	• Investigator-assessed response rates were 8% in arm A and 9% in arm B. • Disease control rates were 29% in arm A and 54% in arm B. • Median time to progression was 1.5 months in arm A and 4.0 months in arm B. • One-year survival was 39% and 33%, and median survival was 7.4 and 7.8 months in arms A and B, respectively. • Adverse effect profiles were as expected in both arms, with no significant additivity. • The most common grade ≥ 3 adverse events were neutropenia, fatigue, and dyspnea (4% and 53%, 19% and 26%, and 17% and 14% of patients in arms A and B, respectively).	Fanucchi et al 2006
Trials of EGFR inhibitors					
Afatinib + BSC Vs. Placebo + BSC	Patients with pathologically confirmed stage IIIB or stage IV adenocarcinoma with measurable disease, had failed one or two lines of chemotherapy, and had disease progression after at least 12 weeks of previous treatment with erlotinib or gefitinib Median age, 58 yrs (n=585)	NR	**P:** OS **S:** PFS, ORR, QOL and toxicity	• Median OS was 10·8 months (95% CI 10·0–12·0) in the afatinib group and 12·0 months (10·2–14·3) in the placebo group (hazard ratio 1·08, 95% CI 0·86–1·35; p=0·74). • Median PFS was longer in the afatinib group (3·3 months, 95% CI 2·79–4·40) than it was in the placebo group (1·1 months, 0·95–1·68; hazard ratio 0·38, 95% CI 0·31–0·48; p<0·0001). • No complete responses to treatment were noted; 29 (7%) patients had a partial response in the afatinib group, as did one patient in the placebo group. • The most common adverse events in the afatinib group were diarrhoea (339 [87%] of 390 patients; 66 [17%] were grade 3) and rash or acne (305 [78%] patients; 56 [14%] were grade 3). These events occurred less often in the placebo group (18 [9%] of 195 patients had diarrhoea; 31 [16%] had rash or acne), all being grade 1 or 2. • Drug-related serious adverse events occurred in 39 (10%) patients in the afatinib group and one (<1%) patient in the placebo group. • There were 2 possibly treatment-related deaths in the afatinib group	Miller et al, 2012
Erlotinib 150 mg/day Vs. Standard	Patients with advanced NSCLC with disease progression after standard platinum based doublet Median age,59 yrs (n=424)	Median, 27·9 months (erlotinib group)	**P:** OS **S:** PFS and time to disease	• Study was halted prematurely because of slow recruitment • Median OS was 5·3 months (95% CI 4·0–6·0) with erlotinib and 5·5 months (4·4–7·1) with chemotherapy	Ciuleanu et al 2012

chemotherapy		24·8 months (chemotherapy group)	progression	(hazard ratio [HR] 0·96, 95% CI 0·78–1·19; log-rank p=0·73). • The adverse-event profile of each group was in line with previous studies. Rash (98/196 [50%] in the erlotinib group vs. 10/213 [5%] in the chemotherapy group for all grades; nine [5%] vs. none for grade 3 or 4) and diarrhea (36 [18%] vs. four [2%] for all grades; five [3%] vs. none for grade 3 or 4) were the most common treatment-related adverse events with erlotinib, whereas alopecia (none vs. 23 [11%] for all grades; none vs. one [<1%] for grade 3/4) was the most common treatment-related adverse event with chemotherapy.	
Sunitinib + Erlotinib Vs. Placebo + Erlotinib	Patients with histologically or cytologically proven advanced NSCLC and with evidence of disease progression following treatment with one or two chemotherapy regimens for advanced stage NSCLC were included Median age, 61 yrs (n=960)	Median, 21.3 and 22.0 months in the Sunitinib + erlotinib and erlotinib alone arms	**P:** OS **S:** PFS, ORR, and toxicity	• Median OS was 9.0 months for sunitinib plus erlotinib versus 8.5 months for erlotinib alone (hazard ratio [HR], 0.922; 95% CI, 0.797 to 1.067; one-sided stratified log-rank P = .1388). • Median PFS was 3.6 months versus 2.0 months (HR, 0.807; 95% CI, 0.695 to 0.937; one-sided stratified log-rank P = .0023), and ORR was 10.6% versus 6.9% (two-sided stratified log-rank P = .0471), respectively. • Treatment-related toxicities of grade 3 or higher, including rash/dermatitis, diarrhea, and asthenia/ fatigue were more frequent in the sunitinib plus erlotinib arm.	Scagliotti et al 2012, 2010 (abstract) & Thongprasert et al 2010 (abstract)
Erlotinib + Entinostat Vs. Erlotinib + Placebo	Patients with histologically or Cytologically confirmed stage IIIB or stage IV NSCLC, had received one or two previous chemotherapy or chemoradiotherapy regimens for advanced NSCLC Median age, 66 yrs (n=132)	NR	**P:** 4 month PFS rate **S:** 6 month PFS rate, PFS, OS and Toxicity	• The 4-month PFS rate was comparable for both groups (EE, 18% v EP, 20%; P = .7). • In the subset of patients with high E-cadherin levels, OS was longer in the EE group compared with the EP group (9.4 v 5.4 months; hazard ratio, 0.35; 95% CI, 0.13 to 0.92; P = .03) with a corresponding trend toward increased PFS. • The adverse event (AE) profile icluded rash, fatigue, diarrhea, and nausea the most common AEs in both groups.	Witta et al 2012
Erlotinib Vs. Docetaxel	Patients with wt EGFR NSCLC (exons 19 and 21) at progression, and previously treated with a first line platinum-based regimen Median age, NR (n=221)	Median, 20 months	**P:** OS **S:** PFS	• There were 199 relapses and 157 deaths reported. • The Kaplan-Meier PFS curves showed a highly significant increase favoring docetaxel (HR 0.70 with 95% CI 0.53-0.94; p = 0.016) over erlotinib regimen. • The HR translated into an estimated absolute difference in 6-months PFS of 12% (16% vs 28%). • Data concerning toxicity were consistent with the literature.	Garassino et al 2012 (TAILOR-abstract)

Pemetrexed Vs. Sunitinib Vs. Pemetrexed + Sunitinib	Patients with Stage IIIB/IV NSCLC, PS 0-1 progressive after first-line chemotherapy Median age, NR (n=128)	Median, 99 weeks	**P:** 18 wk PFS rate **S:** OS, ORR and toxicity	• The 18-week PFS rate in the three arms was: P 51% (38-69), S 36% (24-54), P+S 47% (34-65). • There is an overall statistically significant difference in OS between the three arms (2-sided p=0.0179) with HR 0.65 (95%CI: 0.38-1.13) for P/S; HR 0.47 (95%CI: 0.27- 0.82) for P/P+S. • Median OS was 10.5 mo (8.3-22.5) for P, 7.0 mo (6.0-13.0) for S, 6.7 (4.1-10.4) mo for P+S. • Median PFS was 4.4 mo (1.7-8.8) for P, 3.3 mo (2.7-4.3) for S, 3.7 mo (2.5-4.3) for P+S (p=0.3). • Toxicity was higher in the S-containing arms: Grade 3/4/5 hematologic toxicity: P 5/0/0 (12%), S 8/1/0 (21%), P+S 5/9/0 (36%); Grade 3/4/5 non-hematologic toxicity (excluding disease related deaths): P 6/2/0 (20%), S 21/3/1 (58%), P+S 21/3/1 (63%).	Heist et al 2012 (CALGB 30704-abstract)
Erlotinib + Sorafenib Vs. Erlotinib + Placebo	Patients with pathologic evidence of NSCLC and ECOG performance status between 0 and 2. Patients must have received one to two prior chemotherapy regimens for advanced NSCLC and had measurable disease per RECIST Median age, 65 yrs (n=168)	NR	PFS, ORR and Toxicity	• ORRs for sorafenib/erlotinib and placebo/erlotinib were 8%and 11%, respectively (P=.56); disease control rates were 54% and 38%, respectively (P=.056). • Median PFS was 3.38 months for sorafenib/erlotinib vs. 1.94 months for placebo/erlotinib (hazard ratio, 0.86; 95% CI, 0.60 to 1.22; P = .196). • In 67 patients with EGFR wild-type (WT) tumors, median PFS was 3.38 months for sorafenib/erlotinib versus 1.77 months for placebo/erlotinib (P = .018); median OS was 8 months for sorafenib/erlotinib versus 4.5 months for placebo/erlotinib (P = .019). • Both regimens were tolerable, with modest toxicity increase with sorafenib.	Spigel et al 2011
Erlotinib + Tivantinib (ET) Vs. Erlotinib + Placebo (EP)	Patients with advanced NSCLC and had been previously treated with ≥1 chemotherapy regimen but were naive to EGFR TKIs Median age, 63 yrs (n=167)	Median, 14 months	**P**: PFS **S:** OS, ORR	• Median PFS was 3.8 months for ET and 2.3 months for EP (HR, 0.81; 95% CI, 0.57 to 1.16; P =.24). • Exploratory analysis revealed that the small cohort with KRAS mutations achieved a PFS HR of 0.18 (95% CI, 0.05 to 0.70; interaction P = .006). • Objective responses were seen in 10% of patients on ET, 7% of patients on EP, and in two patients who crossed over from EP to ET, including one with EGFR mutation and MET gene copy number greater than 5. • There were no significant differences in adverse events between study arms.	Sequist et al 2010 (abstract) & 2011 & Schiller et al 2010 (abstract) & Von pawel et al 2010 (abstract)

Gefitinib Vs. Pemetrexed	Eligible patients had a performance status 0 to 2, previous treatment with one prior platinum-based regimen, pulmonary adenocarcinoma, and never-smoking state. Median age, NR (n=135)	NR	**P**: PFS	• Overall response rates were 30.1% and 14.9% (P < 0.001) for gefitinib and pemetrexed, respectively. • PFS was met with 9.4 months for gefitinib versus 2.9 months for pemetrexed, which was significantly different (P = 0.010). • The median overall survival has not been reached yet in both groups. • The 1-year survival rate for gefitinib and pemetrexed arm was 73.6% and 70.5% (P = 0.89), respectively	Ahn et al 2011 (Abstract)
Icotinib Vs. Gefitinib	Patients with NSCLC that has progressed after one or two lines of chemotherapies Median age, NR (n=399)	NR	**P**: PFS **S:** OS, ORR, TTP, QOL and tolerance	• Ic demonstrated 35 day (d) median PFS extension compared to Ge (Ic vs. Ge: 137 d vs. 102, HR 0.84, 95% CI 0.67-1.05). • With 49.4% maturity, OS was similar between Ic and Ge groups (median OS was 504 d and 531 d, respectively). • Furthermore, ORR (Ic vs. Ge: 27.6% vs. 27.2%), DCR (75.4% vs. 74.9%), TTP (156 d vs. 111 d) and QoL (101.4± 9.6 vs. 103.0± 19.1) were comparable between Ic and Ge groups. • Adverse response rate in Ic group was 60.5%, which was significantly lower than that in Ge group (70.4%) (P=0.04). • The ORR and PFS in both Ic and Ge groups demonstrated significant differences between pts with mutations (M) and pts with the wild type gene (W).	Sun et al 2011 (ICOGEN - abstract)
Everolimus + Erlotinib Vs Erlotinib Alone	Patients with advanced, progressive NSCLC, WHO performance status ≤1, and adequate bone marrow and liver function Mean age, 60yrs (n=133)	NR	**P:** DCR at 3 months **S:** OS, PFS, ORR and Toxicity	• DCR (95% CI) at 3 months was 39.4% (27.6-52.2) for combination therapy and 28.4% (18.0-40.7) for monotherapy. • Eight and 7 patients, respectively, achieved a partial response; none achieved a complete response. • ORR (95% CI) was 12.1% (5.4–22.5) for the combination and 10.4% (4.3-20.3) for monotherapy. • Median PFS (95% CI) was 2.9 (2.4-3.9) mo for the combination and 2.0 (1.1-2.8) mo for monotherapy. • More patients had best overall response of stable disease (i.e. SD for ≥6 wks not qualifying for CR, PR) with combination (45.5%) than monotherapy (28.4%). • The most common Grade 3/4 AEs were stomatitis (32%), asthenia (11%), and diarrhea (8%) with the combination and dyspnea (6%) and diarrhea (5%) with monotherapy.	Bennouna et al 2010 (abstract)
Gefitinib vs.	Japanese patients with advanced/metastatic (stage IIIb/IV) or recurrent NSCLC who failed one or	Median, 21 months	QOL	• Gefitinib showed statistically significant benefits over docetaxel in QoL improvement rates (FACT-L 23% versus 14%, P = 0.023; TOI 21%	Sekine 2009 & Maruyama 2008

Docetaxel	two chemotherapy regimens Median age, NR (n=490)			versus 9%, P = 0.002) and mean change from baseline score [mean treatment difference: FACT-L 3.72 points, 95% confidence interval (CI) 0.55–6.89, P = 0.022; TOI 4.31 points, 95% CI 2.13– 6.49, P < 0.001], although differences did not meet the clinically relevant six-point change. • There were no significant differences between treatments in LCS improvement rates (23% versus 20%, P = 0.562) or mean change from baseline score (0.63 points, 95% CI 20.07 to 1.34, P = 0.077).	

Ongoing trials
Retrieved from www.clinicaltrials.gov

Intervention	Official title	Status	Protocol ID	Completion Date	Last updated
Pemetrexed disodium Vs. Sunitinib malate Vs. Pemetrexed disodium + Sunitinib malate	A Randomized Phase II Study to Assess the Efficacy of Pemetrexed or Sunitinib or Pemetrexed Plus Sunitinib in the Second-Line Treatment of Advanced Non-Small Cell Lung Cancer	Recruiting (Estimated N=225)	NCT00698815	August 2010	April 6, 2011
Erlotinib + docetaxel Vs. Docetaxel	Randomized Open Non Comparative Multicenter Phase II Study of Sequential Erlotinib With Docetaxel Versus Docetaxel Alone in Second Line of Treatment in Patients With Non Small Cell Lung Cancer After Failure of First Line Chemotherapy	Recruiting (Estimated N=156)	NCT01350817	December 2013	March 14, 2012

Acronyms: Non–small-cell lung cancer (NSCLC);Primary (P); Secondary (S); Time to progression (TTP); Objective response rate (ORR); Overall survival (OS); Progression free survival (PFS); Response Rate (RR); Lung cancer subscale (LCS); Disease control rate (DCR)

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. No, It doesn't contradict the current recommendation. However, there needs to be some modifications If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. **Go to 2**.
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2. Not entirely. a. The current recommendations cover all relevant subjects, however there is need to update due to the large volume of new evidence identified If both are Yes, the document can be **ENDORSED**. If either is No, **go to 3**.
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	4. No If Yes, a final decision can be **DELAYED** up to one year. If No, **go to 4.**
5. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	6. Yes If Yes, the document needs an **UPDATE**. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically **ARCHIVED**. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.

Review Outcome	UPDATE
DSG/GDG Approval Date	Oct 1, 2012
DSG/GDG Commentary	The existing 2nd line guidelines requires major revision: 1) The role of histology in treatment choice needs to be added. 2) The comparisons of EGFR TKI's to chemotherapy should be included. 3) The role of maintenance therapy should be included.

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Search strategy:

Medline

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.

14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. exp lung neoplasms/
42. (cancer? or carcinoma? or neoplasms? or tumor?).tw.
43. non small cell lung.tw.
44. 42 and 43
45. 41 or 44
46. quality of life.mp. or exp "Quality of Life"/
47. 45 or 46
48. (chemotherapy or systemic therapy).mp.
49. 47 and 48
50. (recurrence? or relapse? or salvage? or rechallenge? or previous treatment?).tw.
51. 49 and 50
52. 40 and 51
53. (200554: or 2006: or 2007: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
54. 52 and 53

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.

20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp lung neoplasms/
37. (cancer? or carcinoma? or neoplasms? or tumor?).tw.
38. non small cell lung.tw.
39. 37 and 38
40. 36 or 39
41. quality of life.mp. or "quality of life"/
42. 40 or 41
43. (chemotherapy or systemic therapy).tw.
44. 42 and 43
45. (recurrence? or relapse? or salvage? or rechallenge? or previous treatment?).tw.
46. 44 and 45
47. 35 and 46
48. (200554$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$).ew.
49. 47 and 48

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: Recurrent NSCLC and (systemic therapy)
Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: Recurrent NSCLC and (systemic therapy)

OUTCOMES DEFINITIONS

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** - A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.