

NON-SMALL CELL LUNG CANCER STAGE IV

Date Developed: July, 2008

Date Revised: September, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Malignancy Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Lung cancer is the overall leading cause of cancer mortality in Canadian men and women. By the end of 2009, an estimated 23,400 new cases of lung cancer will be diagnosed in Canada.¹ In addition, an estimated 20,500 Canadian men and women will die from their disease, a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.¹ Despite many research and clinical advances in lung cancer treatments, the age-standardized five-year survival rate for all types and stages of lung cancer combined is only 15 percent for Canada overall, and 12 percent for Alberta.¹

The economic impact of lung cancer care is equally as staggering. In an analysis of the actual costs associated with the care of patients with lung cancer in Alberta, *Demeter et al.* reported that in 1998, the median cost of services for *each* patient with either non-small cell or small cell lung cancer in Alberta was \$10,928 and \$15,350, respectively.² Smoking remains the largest single risk factor for lung cancer, responsible for 90 percent of lung cancers in men and 80 percent of lung cancers in women in Canada. Exposure to specific industrial and atmospheric pollutants, including second-hand tobacco smoke, also increases an individual's risk of lung cancer.

Lung cancer can be classified into non-small cell lung cancer (NSCLC) or small-cell lung cancer (SCLC). NSCLC accounts for 80 percent of all lung cancer cases, and is categorized using the TNM staging system, which was recently updated by the International Association for the Study of Lung Cancer (IASLC). The staging definitions and stage groups for NSCLC are summarized in a supporting document ([NSCLC Staging System](#)).

Approximately 40 percent of patients with newly diagnosed NSCLC will have stage IV disease.³ This group of patients includes those with locally advanced disease with malignant pleural effusion and those with distant metastases. Treatment options for these subgroups of patients are dependent on the patient's performance status (PS), which has been determined to be an important determinant of treatment outcome.

GUIDELINE GOALS AND OBJECTIVES

- To outline the management recommendations for patients with stage IV non-small cell lung cancer (NSCLC).

GUIDELINE QUESTIONS

- What are the recommended treatment options in patients with stage IV non-small cell lung cancer?

DEVELOPMENT PANEL

This updated **guideline** was reviewed and endorsed by the Alberta Provincial Thoracic Malignancy Tumour Team. Members of the Alberta Provincial Thoracic Malignancy Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Updated **evidence** was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Malignancy Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

For this guideline update, medical journal articles were searched using Medline (1950 to August Week 1, 2009), EMBASE (1980 to August Week 1, 2009), Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Lung Neoplasms [MeSH heading], Carcinoma, Non-Small Cell Lung [MeSH heading], practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published prior to January 2008.

In addition, a search for new or updated practice guidelines published since January 2008 was conducted by accessing the websites of the following organizations: Cancer Care Ontario (CCO), British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), the National Comprehensive Cancer Network (NCCN), the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), the American College of Chest Physicians (ACCP), the Australian Cancer Network, and the European Society for Medical Oncology (ESMO).

TARGET POPULATION

The recommendations in this guideline apply to adult patients over the age of 18 years.

RECOMMENDATIONS

1. Whenever possible patients should be considered for eligibility in ongoing clinical trials.
2. Combination chemotherapy consisting of platinum-based doublets is considered the standard of care for first line treatment of advanced NSCLC. Acceptable alternatives include non-platinum doublets or monotherapy.
3. Second line or subsequent chemotherapy options for advanced NSCLC include docetaxel, erlotinib or pemetrexed.
4. Palliative radiotherapy is recommended for relief of specific symptoms and/or prophylactic prevention of symptom development.
5. Patients with a solitary metastasis as the basis for stage IV disease with good performance status and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy.

DISCUSSION

Combination Chemotherapy

Combination chemotherapy is considered the standard of care for patients with advanced NSCLC and good PS (recommendation #2). In a recent large Cochrane meta-analysis of 13,601 patients with advanced NSCLC, *Delbaldo et al.* compared trials using a doublet regimen with those that used a single-agent regimen and reported that the combination of two chemotherapeutic agents was superior in terms of observed tumour response (OR 0.42, 95% CI 0.37-0.47, $p < .001$) and one-year survival (OR 0.80, 95% CI 0.70-0.91, $p < .001$).⁴ The authors also reported an increased tumour response rate for trials using a triplet regimen compared to a single-agent regimen (OR 0.66, 95% CI 0.58-0.75, $p < .001$), however, there was no improvement in one-year survival associated with the triplet regimen. In addition, the triplet regimen

was associated with a high rate of toxicity. This has led the American College of Chest Physicians (ACCP), as well as Cancer Care Ontario (CCO) to make a recommendation against the use of combinations of three chemotherapeutic agents for the first-line treatment of advanced NSCLC.^{3,5}

While several meta-analyses of large randomized controlled trials have found that platinum-based combination regimens result in significantly higher response rates than non-platinum regimens,⁶⁻⁷ no single combination has been convincingly shown to be superior to another.^{3,5,8-9} In addition, two meta-analyses and one systematic review comparing carboplatin-based versus cisplatin-based chemotherapy for advanced NSCLC reported that the cisplatin-based regimens are associated with a slightly higher survival rate compared carboplatin-based regimens,¹⁰⁻¹² while a third meta-analysis found that there was no survival advantage to cisplatin-based regimens compared to carboplatin-based regimens.¹³ It is the consensus of the Alberta Provincial Thoracic Malignancy Tumour Team that cisplatin in combination with either vinorelbine or gemcitabine is the recommended first-line treatment for patients with advanced NSCLC and a good PS. In individuals with a contraindication to cisplatin, the use of carboplatin is an acceptable alternative. In cases where platinum combinations may be contraindicated, non-platinum combinations or monotherapy are suitable alternatives.

There is an emerging body of research suggesting that the use of agents that block the epidermal growth factor receptor (EGFR), which is a tyrosine kinase receptor, may be beneficial in the treatment of select patients with advanced NSCLC.¹⁴⁻¹⁸ Two large-scale randomized clinical trials, IPASS and INTEREST, have shown that the use of gefitinib, a tyrosine kinase inhibitor, is associated with increases in progression-free survival rates when a mutation of the EGFR gene is present in the tumour.^{14,15} Such mutations are more frequent in the tumours of patients who are never-smokers, females, have adenocarcinomas, and are of East-Asian origin. The role of EGFR tyrosine kinase inhibitors in the treatment of advanced NSCLC is still being defined; *Ellis et al.* recently conducted a systematic literature review and concluded that while there is insufficient evidence at present to recommend single-agent EGFR tyrosine kinase inhibitors as first-line treatment, they do play a role in the treatment of patients with NSCLC who are not candidates for further chemotherapy.¹⁹ Early results suggest that screening patients with NSCLC for EGFR mutations may be beneficial in the treatment decision-making process.²⁰

Results of recent phase III clinical trials have also suggested a benefit to maintenance therapy in select patients with stage IIIB or stage IV NSCLC who have responded to initial chemotherapy and/or who have not progressed after four cycles of platinum-based chemotherapy. At the 2009 American Society of Clinical Oncology (ASCO) meeting, *Belani et al.* reported the final results of a randomized trial comparing 441 patients treated with pemetrexed plus best supportive care (BSC) versus 222 patients who received a placebo plus BSC.²¹ Patients treated with pemetrexed had significantly higher overall survival rates than those treated with a placebo (HR=0.79, 95% CI 0.65-0.95; p=.012), and the therapy was well-tolerated.²¹ Also during the 2009 ASCO meeting, *Miller et al.* reported the preliminary results of a phase IIIb clinical trial comparing therapy with bevacizumab with or without erlotinib following completion of doublet chemotherapy with bevacizumab plus a platinum agent for first-line therapy in patients with stages IIIB or IV NSCLC.²² The progression-free survival rate was significantly higher for the bevacizumab/erlotinib group compared to the bevacizumab alone group (4.8 months versus 3.7 months; HR=0.722, 95% CI 0.592-0.881; p=.0012), and the safety profile was reported to be acceptable.²²

Second-line Therapy

The Alberta Provincial Thoracic Malignancy Tumour Team recommends the use of one of the three agents currently approved for second-line treatment of advanced NSCLC: docetaxel, pemetrexed and erlotinib (recommendation #3). While all three agents have been found to produce similar rates of response and overall survival, the choice of which agent to use depends on factors such as the patient's comorbidities, toxicity from previous treatments, the risk for neutropenia, smoking history, and personal preferences.²³ When compared to either best supportive care, vinorelbine, or ifosfamide, two large phase III clinical trials have established docetaxel at a dose of 75 mg/m² every three weeks as a standard therapy in the second-line setting.^{24,25} In a randomized phase III trial, pemetrexed at a dose of 500 mg/m² demonstrated clinical efficacy similar to that of docetaxel at a dose of 75 mg/m².²⁶ Patients treated with pemetrexed in this trial required supplementation with vitamin B₁₂ (1000 µg every 9 weeks) and folic acid (350–1,000 µg daily).²⁶ The National Cancer Institute of Canada BR.21 trial compared erlotinib with best supportive care in 731 patients who had received one or two prior chemotherapy regimens, and who were not eligible for further chemotherapy.²⁷ Compared to best supportive care, treatment with 150 mg daily erlotinib resulted in statistically significant higher progression-free survival and overall survival rates.²⁷ In a review of the hematologic and non-hematologic toxicities reported in the three clinical trials of docetaxel, pemetrexed, and erlotinib, *Stinchcombe et al.* reported that docetaxel was associated with a significantly higher rate of hematologic toxicities than pemetrexed and erlotinib, which had no significant hematologic toxicity.²³ Pemetrexed and docetaxel were found to have similar rates of non-hematologic toxicities, while erlotinib was found to have a higher rate, predominantly manifesting as fatigue, rash, and diarrhea.²³

Palliative Radiotherapy

Palliative radiotherapy (RT) plays a significant role in the management of patients with advanced NSCLC who are symptomatic either because they have not responded to chemotherapy, have relapsed, or have contraindications to chemotherapy agents. Therefore, the Alberta Provincial Thoracic Malignancy Tumour team recommends that palliative RT be provided to patients for relief or prevention of symptoms related to thoracic malignancy (recommendation #4). The most common symptoms of metastatic disease include cough, dyspnea, hemoptysis, post-obstructive pneumonia, and pain.

There is some debate as to which RT regimen is the most beneficial and least toxic for patients with locally advanced or metastatic NSCLC who are not suitable for radical RT given with curative intent. In a recent Cochrane review, *Lester et al.* reviewed 14 randomized controlled trials and found that no single regimen was superior in terms of palliation of symptoms.²⁸ Although none of the studies reviewed reported a significant increase in survival, higher dose palliative RT was associated with more frequent reports of toxicity and visits to the hospital.²⁸ The authors concluded that in patients with a poor PS, short courses of palliative RT, such as 10 Gy in one fraction or 16-17 Gy in two fractions, were better tolerated. The most frequently reported and serious adverse effect was radiation myelitis, therefore they stressed that care should be taken to either avoid irradiating or reduce the dose to the spinal cord if the 17 Gy/2 fractions dose was used.²⁸ In patients with a good PS, the authors also concluded that higher dose palliative regimens, such as 36 Gy in 12 fractions, could be considered.²⁸ The CCO guideline recommendations for unresected stage III disease state that there is insufficient published evidence to determine the optimal dose or timing of radiotherapy when the goal of therapy is symptom palliation.²⁹ Reasonable treatment options for unresected stage III or locally advanced stage IV disease may include: 20 Gy in 5 fractions, 30 Gy in 10 fractions, 18 Gy in 3 fractions, or 36-39 Gy in 12-13 fractions. Decreased survival and quality of life were associated with single-fraction 10 Gy radiotherapy when compared to 20 Gy in 5 fractions in one multi-centre Canadian clinical trial, therefore this regimen is not recommended.³⁰ However, the Alberta

Provincial Thoracic Malignancy Tumour Team members agree with the CCO consensus that single fractions of radiotherapy less than 10 Gy may be appropriate in some clinical circumstances, such as poor performance status or patient travel distance. In the most recent systematic review of 13 randomized clinical trials involving 3473 patients, *Fairchild et al.* described a statistically significantly improved total symptom score (77.1% vs. 65.4%, $p=.003$) and one-year survival (26.5% vs. 21.7%, $p=.002$) for high-dose versus low-dose palliative thoracic RT.³¹ The authors recommend that consideration of an RT schedule of 35 Gy in 10 fractions is warranted in certain clinical scenarios, provided that the patient is informed of the trade-off between advantages (survival improvement, decreased likelihood of re-irradiation) and disadvantages (higher likelihood of esophagitis, longer time investment).³¹

It is the opinion of the Alberta Provincial Thoracic Malignancy Tumour Team that patients with a solitary metastasis as the basis for stage IV disease, good PS, and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy (recommendation #5).

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACCP	American College of Chest Physicians
ASCO	American Society of Clinical Oncology
BSC	best supportive care
CCO	Cancer Care Ontario
CI	confidence interval
HD	high-dose
HR	hazard ratio
EGFR	epidermal growth factor receptor
IASLC	International Association for the Study of Lung Cancer
INTEREST	Iressa Non-small cell lung cancer Trial Evaluating REsponse and Survival against Taxotere trial
IPASS	Iressa Pan Asia Study
LD	low-dose
NSCLC	non-small cell lung cancer
OR	odds ratio
PS	performance status
RT	radiotherapy
TNM	tumour-node-metastasis

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

REFERENCES

1. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society. ISSN: 0835-2976. Available at: http://www.cancer.ca/canada-wide/about%20cancer/cancer%20statistics/~/_media/CCS/Canada%20wide/Files%20List/English%20files%20heading/pdf%20not%20in%20publications%20section/Stats%202009E%20Cdn%20Cancer.ashx Accessed: August 14, 2009
2. Demeter SJ, Jacobs P, Chmielowiec C, Logus W, Hailey D, Fassbender K, et al. The cost of lung cancer in Alberta. *Can Respir J* 2007 Mar;14(2):81-6.
3. Socinski MA, Crowell R, Hensing TE, Langer CJ, Lilenbaum R, Sandler AB, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence based clinical practice guidelines (2nd edition). *Chest* 2007 Sept;132(suppl 3):277S-289S.
4. Delbaldo C, Michiels S, Rolland E, Syz N, Soria JC, Le Chevalier T, Pignon JP. Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. *Cochrane Database of Systematic Reviews* 2007;issue 4:article number CD004569.
5. Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK, Lung Cancer Disease Group. First line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: guideline recommendations. Evidence Based Series #7-10, Section 1. Cancer Care Ontario Program in Evidence Based Care. Report Date: May 2009. Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=45735> Accessed: August 13, 2009
6. Pujol JL, Barlesi F, Daurès JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. *Lung Cancer* 2006 Mar;51(3):335-45.
7. D'Addario G, Pintilie M, Leigh NB, Feld R, Cerny T, Sheperd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005 May;23(13):2926-36.
8. Le Chevalier T, Scagliotti G, Natale R, Danson S, Rosell R, Stahel R, et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small cell lung cancer: a meta-analysis of survival outcomes. *Lung Cancer* 2005 Jan;47(1):69-80.
9. Douillard JY, Laporte S, Fossella F, Georgoulia V, Pujol LJ, Kubota K, et al. Comparison of docetaxel and vinca alkaloid-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer: a meta-analysis of seven randomized clinical trials. *J Thorac Oncol* 2007 Oct;2(10):939-46.
10. Jiang J, Liang X, Zhou X, Huang R, Chu Z. A meta-analysis of randomized controlled trials comparing carboplatin-based to cisplatin-based chemotherapy in advanced non-small cell lung cancer. *Lung Cancer* 2007 Sept;57(3):348-58.
11. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007 Jun;99(11):847-57.
12. Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. *Lung Cancer* 2008 Jan;59(1):1-11.
13. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small cell lung cancer. *J Clin Oncol* 2004 Oct;22(19):3852-9.
14. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009 Sep;361(10):947-57.
15. Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008 Nov;372(9652):1809-18.
16. Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. *J Clin Oncol* 2005 Apr;23(11):2556-68.
17. Hida T, Ogawa S, Park JC, Park JY, Shimizu J, Horio Y, et al. Gefitinib for the treatment of non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2009 Jan;9(1):17-35.
18. Saijo N, Takeuchi M, Kunitoh H. Reasons for response differences seen in the V15-32, INTEREST and IPASS trials. *Nat Rev Clin Oncol* 2009 May;6(5):287-94.
19. Ellis PM, Morzycki W, Melosky B, Butts C, Hirsh V, Krasnoshtein F, et al. The role of the epidermal growth factor receptor tyrosine kinase inhibitors as therapy for advanced, metastatic, and recurrent non-small cell lung cancer: a Canadian national consensus statement. *Current Oncol* 2009;16(1):27-48.

20. Rosell R, Moral T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor mutations in lung cancer. *N Engl J Med* 2009 Sept;361(10):958-67.
21. Belani CP, Brodowicz T, Ciuleanu T, Kim JH, Krzakowski M, Laack, E, et al. Maintenance pemetrexed (Pem) plus best supportive care (BSC) versus placebo (Plac) plus BSC: a randomized phase III study in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2009 Jun;27(18S):abstract #CRA8000.
22. Miller VA, O'Connor P, Soh C, Kabbinar F. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol* 2009 Jun;27(18S):abstract #LBA8002.
23. Stinchcombe TE and Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist* 2008;13(suppl 1):28-36.
24. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000 May;18(10):2095-2103.
25. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000 Jun;18(12):2354-62.
26. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004 May;22(9):1589-97.
27. Shepherd FA, Rodrigues Pereira J, Ciuleanu T Ciuleanu T, Tan EH, Hirsh V, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005 Jul;353(2):123-32.
28. Lester JF, Macbeth FR, Toy E, Coles B. Palliative radiotherapy regimens for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2006;issue 4:article number CD002143.
29. Okawara G, Mackay JA, Evans WK, Ung YC, Lung Cancer Disease Site Group. Management of unresected stage III non-small cell lung cancer: a clinical practice guideline. Evidence Based Series #7-3. Cancer Care Ontario Program in Evidence-Based Care. Current Report Date: January 2006. Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14206> Accessed: August 12, 2009
30. Bezzak A, Dixon P, Brundage M, Tu D, Palmer MJ, Blood P, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). *Int J Radiat Oncol Biol Phys* 2002 Nov;54(3):719-28.
31. Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezzak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol* 2008 Aug;26(24):4001-11.