

# **NON-SMALL CELL LUNG CANCER STAGE IV**

Date Developed: July, 2008

Dates Revised: September, 2009  
June, 2011

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 2010, an estimated 24,100 new cases of lung cancer were diagnosed in Canada.<sup>1</sup> In addition, an estimated 20,600 Canadian men and women died from their disease, a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.<sup>1</sup> While lung cancer death rates are decreasing among Canadian men, they continue to climb among Canadian women. 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.<sup>2</sup> The economic impact of lung cancer care is equally as staggering: the mean cost associated with the care of each patient diagnosed with lung cancer in Alberta has been reported to be \$15,023 for non-small cell lung cancer, and \$18,243 for small cell lung cancer, not including end of life care.<sup>3</sup> 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.

## GUIDELINE QUESTIONS

1. What is the recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)?
2. What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC?
3. What is the optimal second-line therapy for patients with stage IV NSCLC?
4. What is the role of palliative radiotherapy in the management of patients with stage IV NSCLC?

## DEVELOPMENT

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, thoracic surgeons, nurses, nurse practitioners, pathologists, pulmonologists, 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. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

## SEARCH STRATEGY

For this guideline update, the working group conducted a search for new or updated practice guidelines published since August 2009 by accessing the websites of the following organizations: Cancer Care Ontario, the British Columbia Cancer Agency, Cancer Care Nova Scotia, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the Scottish Intercollegiate Guidelines Network, the National Institute for Health and Clinical Excellence, the American College of Chest Physicians, the British Thoracic Society, the Australian Cancer Network, the Italian Association of Thoracic Oncology, and the European Society for Medical Oncology.

Medical journal articles were searched using the Medline (1950 to February Week 2, 2011), EMBASE (1980 to February Week 2, 2011), Cochrane Database of Systematic Reviews (1<sup>st</sup> Quarter, 2011), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The Medline search terms were: "Lung Neoplasms" [MeSH

heading], “Carcinoma, Non-Small Cell Lung” [MeSH heading], “NSCLC” [keyword], and “non-small cell lung cancer” [keyword]. The search was limited to the following publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. This search strategy was modified as necessary and repeated in each of the other electronic databases. The working group excluded articles from the final review if they had a non-English abstract, were not available through the library system, or were published prior to August 2009.

The working group reviewed the currency and acceptability of all relevant literature and updated published guidelines for the treatment for stage IV non-small cell lung cancer; we then circulated a draft of the updated guideline to the entire provincial tumour team for final feedback and approval.

## TARGET POPULATION

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

## RECOMMENDATIONS

1. Whenever possible, patients with advanced non-small cell lung cancer (NSCLC) should be considered for eligibility in ongoing clinical trials.
2. 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.
3. Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC. The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence.
4. Therapy should be continued for four cycles in most patients, and not more than six cycles in responding patients.
5. Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy
  - For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, or docetaxel is recommended over best supportive care alone.
  - For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, or docetaxel is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet.
6. First-line monotherapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib is recommended for patients with EGFR mutation-positive NSCLC.
7. Testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib, irrespective of their gender, ethnicity, and smoking status.
8. Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with any histology, irrespective of EGFR mutational status, or pemetrexed for patients with adenocarcinoma histology.
9. Palliative radiotherapy is recommended for relief of specific symptoms and prophylactic prevention of symptom development.

## DISCUSSION

### Diagnosis and Classification

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).<sup>4</sup> 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.<sup>5</sup> This group includes patients with locally advanced disease with malignant pleural effusion, as well as patients with distant metastases. Decisions regarding the treatment strategy should take into account the patient's age, performance status (PS), comorbidities, prior therapy, and the presence or absence of epidermal growth factor receptor (EGFR) mutations.<sup>6</sup> 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 (recommendation #2).

### Chemotherapy

The type and number of chemotherapy drugs used for the treatment of patients with stage IV disease has been evaluated extensively in randomized controlled trials and meta-analyses.

**Combination chemotherapy.** Two-drug combination chemotherapy with a platinum-based regimen is the standard of care for patients with advanced NSCLC and a PS of 0-1 (recommendation #3). In a large Cochrane meta-analysis involving 13,601 patients with advanced NSCLC, Delbaldo and colleagues compared randomized 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,  $p<0.001$ ) and one-year survival (OR=0.80; 95% CI 0.70-0.91,  $p<0.001$ ).<sup>7</sup> Although the authors also reported an increased tumour response rate for trials using triplet regimens compared to single-agent regimens (OR=0.66; 95% CI 0.58-0.75,  $p<0.001$ ), there was no corresponding improvement in one-year survival associated with triplet therapy, and the triplet regimens were associated with significantly higher rates of toxicity.<sup>7</sup> In a recent phase II-III study published after the Cochrane meta-analysis, 324 patients with advanced NSCLC were randomized to receive either carboplatin plus paclitaxel or carboplatin plus paclitaxel plus gemcitabine.<sup>8</sup> While the investigators reported significant increases in time to progression and median overall survival in favour of the triplet regimen, they also documented significantly higher rates of grade 3-4 toxicity.<sup>8</sup> Improved response rates in patients treated with a cisplatin-containing triplet regimen were also documented in a recent multicentre phase III trial.<sup>9</sup> In this study, patients were randomized to receive either gemcitabine plus vinorelbine with or without cisplatin, or gemcitabine plus paclitaxel with or without cisplatin. Progression-free and overall survival rates were similar in all patients, and triplet therapy was associated with significantly more toxic effects.<sup>9</sup> Based on the high rates of toxicity and conflicting survival outcomes reported in published studies to date, members of the Alberta Provincial Thoracic Malignancy Tumour Team do not currently recommend the combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC (recommendation #3).

**Platinum-based chemotherapy.** Several systematic reviews and meta-analyses have concluded that platinum-based combination regimens result in significantly higher response rates than non-platinum regimens;<sup>10-12</sup> to date, however, there is debate regarding whether any single combination is superior.

Comparisons of carboplatin- versus cisplatin-based chemotherapy for advanced NSCLC have reported that cisplatin-based regimens are associated with higher overall response rates and, in certain subgroups such as nonsquamous NSCLC, a slightly higher survival rate when combined with a third-generation agent compared to carboplatin-based regimens.<sup>13-16</sup> However, carboplatin has the advantage of being easier to administer in an outpatient setting, and may also be associated with a more favourable toxicity profile compared to cisplatin.<sup>17,18</sup>

Cisplatin or carboplatin have been shown to be effective in patients with a good PS (0-1) when combined with any of the following third-generation cytotoxic drugs: gemcitabine, vinorelbine, docetaxel, paclitaxel, and irinotecan. In the ECOG 1594 trial, treatment with cisplatin/gemcitabine was associated with longer progression-free survival when compared to cisplatin/paclitaxel, cisplatin/docetaxel, or carboplatin/paclitaxel.<sup>19</sup> There were no differences in response rates or median survival among the four regimens, however. Similar results were reported in a Japanese trial comparing cisplatin/irinotecan, carboplatin/paclitaxel, cisplatin/gemcitabine, and cisplatin/vinorelbine regimens: the four regimens were all associated with similar response and overall survival rates, but all had different toxicity profiles.<sup>20</sup> In a recent phase III trial, Scagliotti and colleagues randomized chemotherapy-naïve patients with stage IIIB or IV NSCLC to receive either cisplatin/gemcitabine or cisplatin/pemetrexed.<sup>21</sup> Patients with squamous cell histology had significantly better median survival when treated with cisplatin/gemcitabine versus cisplatin/pemetrexed therapy (10.8 vs. 9.4 months). However, in patients with adenocarcinoma and large-cell carcinoma histologies, treatment with cisplatin/pemetrexed was associated with significantly better overall survival compared to treatment with cisplatin/gemcitabine (12.6 vs. 10.9 months, adenocarcinoma; 10.4 vs. 6.7 months, large-cell carcinoma). Grade 3 or 4 nausea was more common in patients treated with cisplatin/pemetrexed, but all other rates of grade 3 or 4 toxicities were significantly lower. Based on these results, several published guidelines now recommend the use of cisplatin/pemetrexed as first-line therapy in patients with nonsquamous histology.<sup>6,22,23</sup> Other published guidelines, however, state that while the Scagliotti *et al.* trial results are sufficient to recommend that pemetrexed not be used in the first-line treatment of patients with squamous histology, the data are not sufficient to recommend that pemetrexed be used preferentially over other agents such as gemcitabine as part of doublet therapy for first-line treatment of patients with adenocarcinoma histology.<sup>24</sup> Pending confirmatory trials, pemetrexed is only approved for second-line use in Alberta at the present time.

It is the consensus of the Alberta Provincial Thoracic Malignancy Tumour Team that cisplatin combined with either vinorelbine or gemcitabine is the recommended first-line treatment for patients with advanced NSCLC and PS 0 or 1. Therapy should be continued for four cycles in most patients, and not more than six cycles in responding patients.<sup>6,17,22,24</sup> The use of carboplatin is an acceptable alternative for patients with a contraindication to cisplatin (recommendation #4). In cases where platinum combinations may be contraindicated, non-platinum combinations are suitable alternatives (recommendation #5).

**Single agent chemotherapy.** With the exception of therapy with EGFR tyrosine-kinase inhibitors in select patients, single agent chemotherapy as first-line treatment is generally limited to elderly patients unable to tolerate combination chemotherapy, as well as patients with a borderline PS (PS=2). In a recent meta-analysis, Baggstrom *et al.* analyzed five trials comparing monotherapy with the third-generation cytotoxic drugs vinorelbine, gemcitabine, paclitaxel, or docetaxel versus best supportive care (BSC).<sup>25</sup> One-year survival rates favoured the third-generation drugs over BSC, with a 7 percent absolute difference of risk between the two groups, and a one-year survival ranging from 24 to 32 percent. In addition, the authors analyzed four trials comparing monotherapy with a third-generation drug versus platinum-based doublet therapy with a second-generation drug. Monotherapy with the third-generation drugs was associated with a slightly lower response rate, but one-year survival rates were comparable for all trials.<sup>25</sup>

For patients with a borderline PS, single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, or docetaxel is recommended over BSC alone; there is no strong evidence to suggest the superiority of one specific third-generation single agent over another (recommendation #5). Docetaxel is currently only approved for second-line therapy in Alberta.

Elderly patients ( $\geq 70$  years) with a PS of 0-1 and no significant comorbidities seem to benefit from combination chemotherapy with a platinum-based doublet.<sup>5,26-28</sup> For elderly patients who cannot tolerate a platinum-based combination, the single agents vinorelbine, gemcitabine, and docetaxel are all viable options that are associated with improved survival and quality of life when compared to BSC alone (recommendation #5).<sup>5</sup>

**EGFR tyrosine kinase inhibitors.** In 2004, several publications identified that a significant number of patients with NSCLC who achieved an objective response after treatment with the tyrosine kinase inhibitors gefitinib or erlotinib harboured activating somatic mutations in the EGFR gene.<sup>29-32</sup> In addition, in a key 2009 publication, Rosell and colleagues screened 2105 patients with NSCLC and identified 350 (16.6%) with EGFR mutations; mutations were more frequent in women, never-smokers, and patients with adenocarcinoma histology.<sup>33</sup> To date, the results of six large randomized phase III trials have been conducted comparing either gefitinib or erlotinib to platinum-based chemotherapy as a first-line treatment for patients with advanced NSCLC (Table 1).<sup>34-40</sup> In two of the gefitinib trials, patients were selected on the basis of the clinical characteristics identified in the Rosell *et al.* study; in the other two gefitinib trials, only patients with confirmed positive EGFR mutational status were included. In all four gefitinib trials, the administration of first-line gefitinib was associated with longer progression-free survival in EGFR-positive patients. In addition, gefitinib therapy was also associated with higher objective response rates, better quality of life, and a more tolerable side-effect profile. Similar results were described in a preliminary report from the OPTIMAL study, in which patients with EGFR mutations were randomized to first-line therapy with either erlotinib or carboplatin-gemcitabine.<sup>40</sup> Preliminary results from the prospective phase III EURTAC trial involving Caucasian patients with a positive EGFR mutational were also recently reported by Rosell and colleagues. Patients treated with erlotinib showed significantly better response and progression-free survival rates when compared to patients treated with platinum-based chemotherapy.<sup>39</sup>

Based on the data published to date, members of the Alberta Provincial Thoracic Malignancy Tumour Team recommend the use of gefitinib as a first-line therapy for patients with confirmed EGFR-positive mutational status (recommendation #6). Gefitinib is currently approved by Health Canada for the first-line treatment of EGFR-mutation positive patients with locally advanced or metastatic NSCLC not amenable to curative therapy. At the present time, gefitinib therapy is under review for funding in Alberta. Erlotinib therapy is currently approved only for second-line treatment of advanced NSCLC in Alberta.

**Table 1.** Summary of Phase III Clinical Trials Assessing First-Line Monotherapy with Gefitinib or Erlotinib in Patients with Advanced NSCLC and Positive EGFR Mutational Status.

Author, Year	Inclusion Criteria	Disease Stage	N	Treatment	Median PFS (months)	Median OS (months)
<b>Gefitinib Therapy</b>						
Mitsudomi, 2010 <sup>34</sup>	CT-naïve, $\leq 75$ years, PS 0-1, Japanese, EGFR-positive	IIIB, IV, or post-op recurrence	88	gefitinib 250mg/day q21 days x 3-6 cycles	9.2	30.9
(West Japan Oncology Group)			89	cisplatin 80mg/m <sup>2</sup> + docetaxel 60mg/m <sup>2</sup> q21 days x 3-6 cycles	6.3 HR=0.489; 95% CI 0.336-0.71, p<0.001	not reached HR=1.638; 95% CI 0.749-3.582, p=0.211

Author, Year	Inclusion Criteria	Disease Stage	N	Treatment	Median PFS (months)	Median OS (months)
<b>Gefitinib Therapy</b>						
Maemondo, 2010 <sup>35</sup>  (North East Japan Study Group)	CT-naïve, <75 years, PS 0-1, EGFR-positive	IIIB, IV, or post-op recurrence	114	gefitinib 250mg/day q21 days	10.8	30.5
			114	carboplatin AUC6 + paclitaxel 200mg/m <sup>2</sup> q21 days	5.4 HR=0.30; 95% CI 0.22-0.41, p<0.001	23.6 p=0.31
Mok, 2009 <sup>36,37</sup>  (IPASS)	CT-naïve, adenocarcinoma, non- or former light smoker	IIIB, IV	132*	gefitinib 250mg/day q21 days x 6 cycles	9.5	21.6
			129*	carboplatin AUC5-6 + paclitaxel 200mg/m <sup>2</sup> q21 days x 6 cycles	6.3 HR= 0.45; 95% CI 0.36-0.64, p<0.001	21.9 HR=1.002; 95% CI 0.756-1.328, p=0.990
Lee, 2009 <sup>38</sup>  (First SIGNAL)	CT-naïve, adenocarcinoma, PS 0-2, never-smoker	IIIB, IV	26*	gefitinib 250mg/day	8.4	30.6
			16*	cisplatin 80mg/m <sup>2</sup> day1, q21 days x 9 cycles + gemcitabine 1250mg/m <sup>2</sup> days1,8	6.7 HR=0.613; 95% CI 0.308-1.221, p=0.084	26.5 HR=0.823; 95% CI 0.352-1.922, p=0.648
<b>Erlotinib Therapy</b>						
Rosell, 2011 <sup>39</sup>  (EURTAC)	CT-naïve, PS 0-2, Caucasian, EGFR-positive	advanced	77	erlotinib	9.4	22.9
			76	platinum-based chemotherapy	5.2 HR=0.42; p<0.0001	18.8 HR=0.80; p=0.42
Zhou, 2010 <sup>40</sup>  (OPTIMAL)	CT-naïve, PS 0-2, EGFR-positive	advanced	82	erlotinib 150 mg/day until unacceptable toxicity or PD	13.1	not reported
			76	carboplatin AUC5 + gemcitabine 1000 mg/m <sup>2</sup> days 1,8 q21 days x 4 cycles	4.6 HR=0.16; 95% CI 0.10-0.26, p<0.0001	

**Abbreviations.** PFS=progression-free survival, OS=overall survival, CT=chemotherapy, PS=performance status, HR=hazard ratio, CI=95% confidence interval, AUC=area under the curve, PD=progressive disease.

\* Subset of patients in trial with positive EGFR mutational status; patients not pre-selected for mutational status.

**EGFR testing.** In addition to the trials outlined in Table 1, multiple retrospective analyses published since 2004 have confirmed that a mutation in the EGFR tyrosine kinase domain is the best predictor of response and progression-free survival to an EGFR tyrosine kinase inhibitor such as gefitinib or erlotinib for first-line treatment of advanced NSCLC. Higher mutation rates have been reported in studies involving Japanese patients, with values ranging from 30 to almost 40 percent.<sup>30,41-45</sup> In Caucasian populations, the rate of EGFR mutations has been reported to range between 7 and 17 percent.<sup>30,33,46,47</sup>

As reported by Rosell *et al.*,<sup>33</sup> EGFR mutations are more common in females and never-smokers with adenocarcinoma tumour histology, however a significant proportion of patients with these clinical characteristics do not harbour an EGFR mutation, and would therefore not benefit from therapy with an EGFR tyrosine kinase inhibitor. In a recently published analysis of 2142 lung adenocarcinoma specimens, D'Angelo and colleagues reported that EGFR mutations in former or current smokers represented 40 percent of all those detected (201/503; 95% CI 36-44%), and that EGFR mutations in men represented 31 percent of all those detected (157/503; 95 CI 27-35%).<sup>48</sup> The overall survival of men and ever-smokers

with EGFR mutations was similar to that seen in women and never-smokers, which led the investigators to conclude that it is the presence of an EGFR mutation and **not** the clinical characteristic that impacts the outcomes of EGFR tyrosine kinase inhibitor treatment. In addition, the investigators reported that 31 percent of all EGFR mutations would be missed if testing were restricted to women only, 40 percent would be missed if testing were restricted to never-smokers only, and 57 percent would be missed if testing were restricted to women who were never-smokers only.<sup>48</sup> On the basis of this body of literature, and in agreement with recommendations recently made by the American Society of Clinical Oncology,<sup>49</sup> members of the Alberta Provincial Thoracic Malignancy Tumour Team agree that testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib or erlotinib, irrespective of their gender, ethnicity, and smoking status (recommendation #7).

**Maintenance chemotherapy.** Recent phase III clinical trials have reported a survival benefit associated with maintenance therapy in select patients with stage IIIB or IV NSCLC who have responded to initial chemotherapy and/or who have not progressed after four cycles of platinum-based chemotherapy. In one randomized double-blind study, Ciuleanu and colleagues compared 441 patients treated with maintenance pemetrexed plus BSC to 222 patients who received BSC alone; all patients had stage IIIB or IV disease and had not progressed after four cycles of platinum-based chemotherapy.<sup>50</sup> Pemetrexed was associated with improved progression-free survival (4.3 vs. 2.6 months; HR=0.50; 95% CI 0.42–0.61,  $p<0.0001$ ) and overall survival (13.4 vs. 10.6 months; HR=0.79; 95% CI 0.65–0.95,  $p=0.012$ ) compared with placebo. The improvements in progression-free and overall survival were recorded mainly in patients with nonsquamous histology; more specifically, in a *post hoc* intention-to-treat analysis, median progression-free survival for the 328 patients with adenocarcinoma histology was significantly better for those treated with pemetrexed versus placebo (4.7 vs. 2.6 months; HR=0.45, 95% CI 0.35–0.59;  $p<0.0001$ ). Similarly, in the SATURN trial, patients were randomized to receive maintenance therapy with either erlotinib ( $n=438$ ) or placebo ( $n=451$ ) if they did not have progressive disease following four cycles of platinum-based chemotherapy.<sup>51</sup> The median progression-free survival was significantly longer for patients treated with erlotinib versus placebo (12.3 vs. 11.1 months; HR=0.71; 95% CI 0.62–0.82,  $p<0.0001$ ). For patients with EGFR-positive immunohistochemistry, those who were treated with erlotinib had a significantly longer progression-free survival compared to those treated with placebo. Fidias *et al.* reported the results of a phase III randomized trial involving patients with stage IIIB or IV disease who were treated with first-line gemcitabine and carboplatin.<sup>52</sup> After four cycles, patients who had not progressed were randomly assigned to immediately receive six cycles of docetaxel or to follow the standard of care, which was defined as no additional therapy until disease progression, at which point they received docetaxel. Treatment with immediate docetaxel was associated with a significantly longer progression-free survival than treatment with delayed docetaxel (5.7 vs. 2.7 months,  $p=0.0001$ ); there was also a non-significant trend toward improved survival with immediate docetaxel compared with delayed docetaxel (12.3 vs. 9.7 months,  $p=0.0853$ ). Notably, while 95 percent of patients in the immediate treatment arm received at least one cycle of docetaxel, only 63 percent of patients in the delayed arm actually went on to receive docetaxel at progression. Median survival for the patients in the delayed arm who actually received docetaxel was equivalent to the 12.5 month survival of the patients in the immediate arm, suggesting that the patients in the immediate docetaxel arm trended toward improved overall survival because more patients were able to receive an active drug.

**Second-line chemotherapy.** The Alberta Provincial Thoracic Malignancy Tumour Team recommends therapy with single-agent docetaxel or erlotinib for patients with an unselected tumour histology, or single-agent pemetrexed for patients with adenocarcinoma tumour histology in the second-line treatment of advanced NSCLC (recommendation #8). All three agents have been reported to produce similar rates of

response and overall survival, therefore the choice of which agent to use will depend on the patient's tumour histology, comorbidities, toxicity from previous treatments, risk for neutropenia, smoking history, and patient convenience and preference.<sup>53</sup>

When compared to either BSC, vinorelbine, or ifosfamide, two phase III randomized trials, TAX317 and TAX320, have established docetaxel at a dose of 75 mg/m<sup>2</sup> every three weeks as a standard therapy in the second-line setting.<sup>54,55</sup> In the TAX317 trial, treatment with 75 mg/m<sup>2</sup> docetaxel was associated with longer time to disease progression, longer median survival, and a better one-year survival rate when compared to BSC.<sup>54</sup> In a follow-up analysis from the TAX317 trial, Dancey and colleagues reported that patients treated with docetaxel had improved pain control and less deterioration in quality of life compared to those receiving BSC, in whom pain control worsened.<sup>56</sup> In the TAX320 trial, overall survival was not significantly different in patients treated with 75 mg/m<sup>2</sup> docetaxel, 100 mg/m<sup>2</sup> docetaxel, vinorelbine, or ifosfamide. However, the one-year survival rate was significantly higher for patients treated with 75 mg/m<sup>2</sup> docetaxel.<sup>55</sup> In an effort to minimize toxicity, weekly administration of docetaxel has been compared to the standard three-week schedule in recent phase II and III clinical trials.<sup>57-62</sup> In a meta-analysis of individual patient data from five trials, Di Maio *et al.* reported no difference in the median survival times for patients receiving docetaxel every three weeks versus weekly (27.4 vs. 26.1 weeks; HR=1.09; 95% CI 0.94-1.26, p=0.2449).<sup>63</sup> In addition, one-year survival rates were 24.8 and 27.0 percent for patients treated every three weeks versus weekly, respectively. Weekly therapy was associated with a significantly lower rate of both severe and febrile neutropenia, but rates of anemia, thrombocytopenia, and non-hematologic toxicity were similar for both treatment schedules. Weekly docetaxel is an acceptable alternative to the standard schedule, particularly for patients at risk for neutropenia, however, weekly administration may be more inconvenient for the patient, and also requires more frequent use of steroids.

In the first phase III randomized trial of second-line pemetrexed in patients with advanced NSCLC, Hanna and colleagues reported similar median overall survivals (8.3 vs. 7.9 months) and one-year survival rates (29.7%) for patients treated with pemetrexed versus docetaxel.<sup>64</sup> Pemetrexed was associated with significantly fewer side effects when compared with docetaxel, particularly grade 3-4 neutropenia, febrile neutropenia, neutropenia with infection, and alopecia.<sup>64</sup> Patients treated with pemetrexed in this trial required supplementation with vitamin B<sub>12</sub> (1000 µg every 9 weeks) and folic acid (350–1,000 µg daily). In a subsequent analysis, patients with non-squamous histology (n=302 adenocarcinoma, n=47 large-cell carcinoma, n=50 other histology) had a longer median overall survival when treated with pemetrexed compared to docetaxel (9.3 vs. 8.0 months; HR=0.78; 95% CI 0.61-1.00, p=0.047). In contrast, patients with squamous histology had a shorter median overall survival when treated with pemetrexed compared to docetaxel (6.2 vs. 7.4 months; HR=1.56, 95% CI 1.08–2.26, p=0.018).<sup>65</sup> In a separate retrospective analysis of this trial, Weiss and colleagues reported that the elderly patients treated with pemetrexed had a slightly longer time to progression and median overall survival than elderly patients treated with docetaxel, although the difference was not statistically significant.<sup>66</sup> Febrile neutropenia was less frequent in elderly patients treated with pemetrexed compared with docetaxel (2.5 vs. 19%, p=0.025). Because of its good toxicity profile, patients with non-squamous histology, including those who are elderly or have a borderline PS, may benefit from second-line therapy with pemetrexed.

The National Cancer Institute of Canada BR.21 trial compared treatment with erlotinib to BSC in 731 patients who had received one or two prior chemotherapy regimens and who were not eligible for further chemotherapy.<sup>67</sup> Compared to BSC, patients treated with 150 mg daily erlotinib had significantly higher progression-free survival (2.2 vs. 1.8 months; HR=0.61, 95% CI 0.5-0.74; p<0.001) and higher overall survival (6.7 vs. 4.7 months; HR=0.70; 95% CI 0.58-0.85, p<0.001).<sup>67</sup> Erlotinib therapy was well-tolerated by the patients; the most common toxic effects were rash and diarrhea. Patients who were never-smokers (p<0.001), female (p=0.006), Asian (p=0.02), had adenocarcinoma histology (p<0.001), and were positive

for EGFR expression ( $p=0.1$ ) were most likely to respond to erlotinib therapy.<sup>67,68</sup> Preliminary findings from the multicentre, open-label phase III TITAN trial were also recently published.<sup>69</sup> In this trial, patients with progressive disease following four cycles of platinum-based doublet therapy were randomized to receive either 150 mg daily of erlotinib ( $n=203$ ) or a standard regimen of either docetaxel ( $n=116$ ) or pemetrexed ( $n=105$ ). There were no significant differences in progression-free survival for patients treated with erlotinib versus docetaxel or pemetrexed (6.3 vs. 8.6 weeks; HR=1.19; 95% CI 0.97-1.46,  $p=0.09$ ), and overall survival was also similar in both groups of patients (5.3 vs. 5.5 months; HR= 0.96; 95% CI 0.78-1.19,  $p=0.73$ ). Erlotinib treatment was associated with a higher incidence of treatment-related adverse events compared to standard treatment (58.2% vs. 40.8%), but most of these adverse events were grade 1-2 rash and diarrhea. There was a lower rate of serious adverse events in patients treated with erlotinib versus standard chemotherapy (1% vs. 6.6%), as well as adverse events leading to death (1.5% vs. 5.2%).<sup>69</sup>

**Trial data.** Bevacizumab is a monoclonal antibody that binds vascular endothelial growth factor (VEGF). Two phase III trials assessing the use of bevacizumab for the treatment of advanced NSCLC have been published to date. In the ECOG 4599 trial, 878 previously untreated patients with non-squamous histology were randomized to treatment with carboplatin-paclitaxel or carboplatin-paclitaxel-bevacizumab.<sup>70</sup> Bevacizumab therapy was associated with significant benefits in overall survival (12.3 vs. 10.3 months; HR for death=0.79; 95% CI 0.67-0.92,  $p=0.003$ ), progression-free survival (6.2 vs. 4.5 months; HR for disease progression=0.66; 95% CI 0.57-0.77,  $p<0.001$ ), and response rate (35% vs. 15%,  $p<0.001$ ). However, treatment-related deaths were more common with bevacizumab therapy (15 vs. 2 deaths,  $p=0.001$ ); in addition, the rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were all significantly higher in the patients who received bevacizumab ( $p<0.05$ ).<sup>70</sup> Similar results were reported by Reck and colleagues in the AVAiL trial, in which 1043 previously untreated patients with advanced non-squamous NSCLC were randomized to treatment with cisplatin-gemcitabine plus either low-dose bevacizumab, high-dose bevacizumab, or placebo.<sup>71,72</sup> Progression-free survival was significantly better in both the low- and high-dose bevacizumab treatment groups compared to placebo, with median progression-free survivals of 6.7, 6.5, and 6.1 months for the low-dose, high-dose, and placebo groups, respectively. When compared to placebo treatment, hazard ratios were 0.75 ( $p=0.003$ ) in the low-dose group and 0.82 ( $p=0.03$ ) in the high-dose group.<sup>71</sup> The benefits for progression-free survival were maintained at 13 months, but the addition of bevacizumab did not have a significant effect on overall survival.<sup>72</sup>

Cetuximab is a monoclonal antibody that binds to the EGFR. In the phase III randomized FLEX trial, 1125 previously untreated patients with advanced NSCLC and positive EGFR expression were randomized to receive therapy with either cisplatin-vinorelbine or cisplatin-vinorelbine-cetuximab.<sup>73</sup> The addition of cetuximab was associated with a significant improvement in overall survival (11.3 vs. 10.1 months; HR=0.87; 95% CI 0.762-0.996,  $p=0.044$ ), but not progression-free survival. Cetuximab therapy was associated with significant increases in toxicity, including rash, febrile neutropenia, diarrhea, and infusion-related reactions. In the phase III BMS-099 trial, Lynch and colleagues randomized chemotherapy-naïve patients with advanced disease to treatment with carboplatin plus a taxane (paclitaxel or docetaxel) or carboplatin-taxane-cetuximab.<sup>74</sup> There were no restrictions by histology or EGFR status in this trial. The addition of cetuximab was not associated with significant improvements in either progression-free survival or overall survival. Ongoing trials examining bevacizumab or cetuximab should help to further define the role of these drugs for the treatment of NSCLC. At the present time, neither cetuximab nor bevacizumab are approved for the treatment of advanced NSCLC in Alberta.

Crizotinib is an anaplastic lymphoma kinase (ALK) inhibitor under study in patients with advanced NSCLC expressing the EML4-ALK fusion gene; this gene is present in approximately two to seven percent of such tumours, and is mutually exclusive with K-Ras and EGFR mutations.<sup>75</sup> In a recent phase I study, Kwak and colleagues reported a response rate of 57 percent and a stable disease rate of 33 percent in 82 patients with advanced NSCLC who were treated with second-, third-, or fourth-line crizotinib.<sup>76</sup> The results of this early trial are promising, and, along with other clinical trials currently underway, may strengthen support for the role of prospective genotyping in the selection of therapy for patients with advanced NSCLC.

### Palliative Radiotherapy

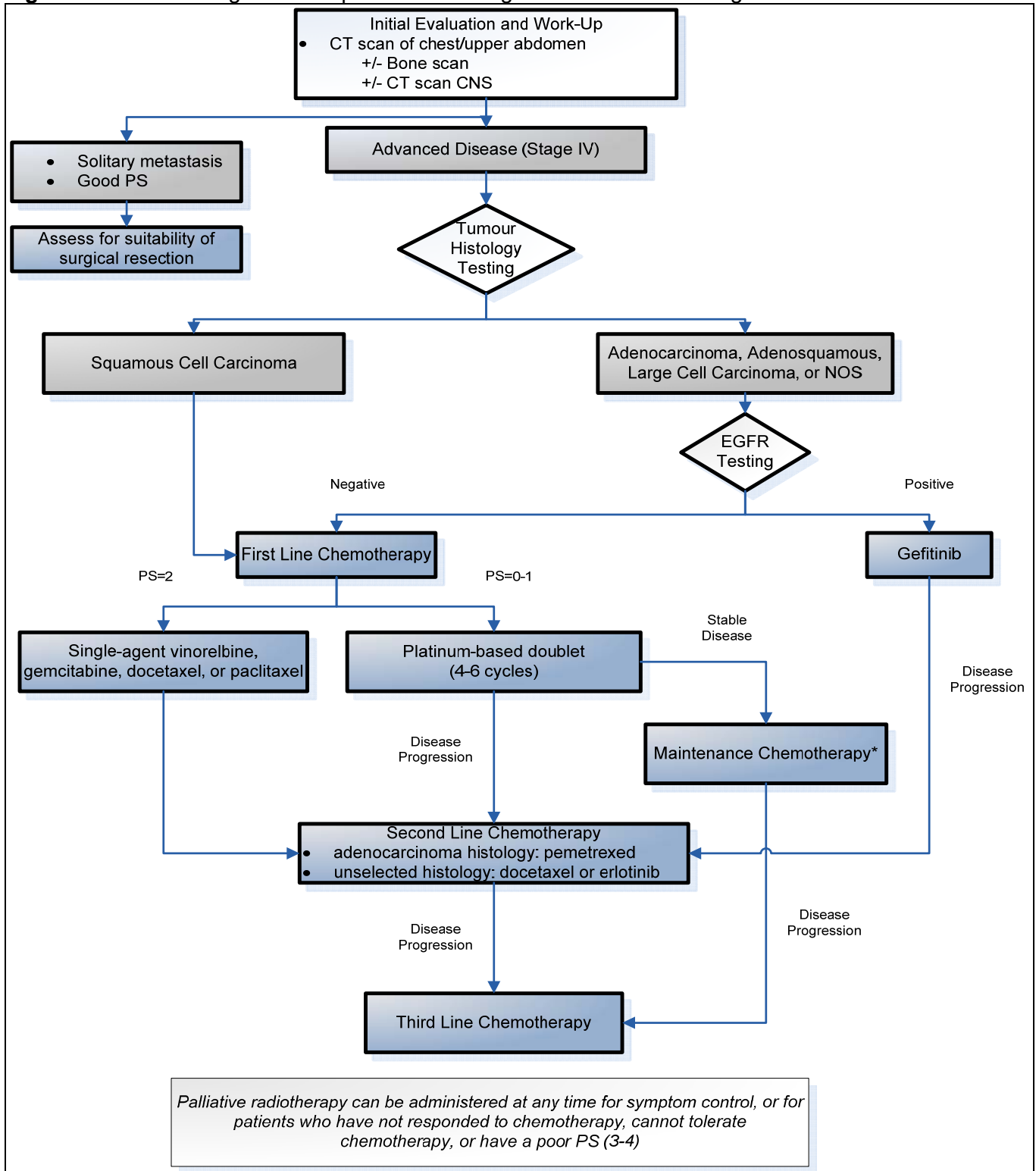
Palliative radiotherapy plays a significant role in the management of patients with advanced NSCLC who are symptomatic either because they have not responded to chemotherapy, have relapsed, or have contraindications to chemotherapy agents. Palliative radiotherapy should be provided to patients for relief and prevention of symptoms related to advanced NSCLC, including cough, dyspnea, hemoptysis, post-obstructive pneumonia, and pain (recommendation #9).

There is some debate as to which radiotherapy regimen is the most beneficial and least toxic for patients with locally advanced or metastatic NSCLC who are not suitable for curative-intent radical radiotherapy. In a recent Cochrane review, Lester *et al.* reviewed 14 randomized controlled trials and reported that no single regimen was superior in terms of palliation of symptoms.<sup>77</sup> Although none of the studies reviewed reported a significant increase in survival, higher dose palliative radiotherapy was associated with more frequent reports of toxicity and visits to the hospital. The authors concluded that in patients with a poor PS (3-4), short courses of palliative radiotherapy, 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.<sup>77</sup> In patients with a good PS (0-1), the authors also concluded that higher dose palliative regimens, such as 36 Gy in 12 fractions, could be considered.<sup>77</sup>

There is insufficient published evidence to determine the optimal dose or timing of radiotherapy for patients with advanced NSCLC when the goal of therapy is symptom palliation. Reasonable treatment options 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.<sup>78</sup> In one multi-centre trial, decreased survival and quality of life were associated with single-fraction 10 Gy radiotherapy compared to 20 Gy in 5 fractions, therefore this regimen is not recommended.<sup>79</sup> However, the Alberta Provincial Thoracic Malignancy Tumour Team members agree that single fractions of radiotherapy less than 10 Gy may be appropriate in some clinical circumstances, such as poor PS (3-4) or patient travel distance. In a 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 radiotherapy.<sup>80</sup> The authors recommend that consideration of a 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).<sup>80</sup> For a detailed review and treatment recommendations regarding palliative radiotherapy, please refer to the [Palliative Radiotherapy Clinical Practice Guideline](#).

Figure 1 summarizes the treatment options recommended by the Alberta Thoracic Malignancy Tumour Team for patients with stage IV NSCLC.

**Figure 1.** Treatment algorithm for patients with stage IV non-small cell lung cancer.



\* Maintenance chemotherapy with pemetrexed is currently pending funding and approval by Alberta Health and Wellness.

## GLOSSARY OF ABBREVIATIONS

Acronym	Description
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
AVAIL	Avastin in Lung Cancer trial
BSC	best supportive care
CI	confidence interval
CT	computed tomography scan
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-associated protein-like 4 gene
Gy	gray
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
IDEAL	Iressa Dose Evaluation in Advanced Lung Cancer trial
ISEL	Iressa Survival Evaluation in Lung Cancer trial
NSCLC	non-small cell lung cancer
OR	odds ratio
PET	positron emission tomography scan
PFT	pulmonary function testing
PS	performance status
SATURN	Sequential Tarceva in Unresectable NSCLC trial
TITAN	Tarceva in Treatment of Advanced NSCLC trial
TNM	tumour-node-metastasis
VEGF	vascular endothelial growth factor
VQ	ventilation/perfusion scan

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Thoracic Malignancy Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Thoracic Malignancy Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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