NON-SMALL CELL LUNG CANCER
STAGE IV

Effective Date: November, 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic 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 2012, an estimated 25,600 new cases of lung cancer were diagnosed in Canada.[1] In addition, an estimated 20,200 Canadian men and women died from their disease, a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.[1] In 2012, lung cancer was the leading cause of cancer death for both men and women in Alberta.[1] Indeed, while lung cancer death rates are decreasing among Canadian men, they continue to climb among Canadian women. Despite much research and many clinical advances in lung cancer treatments, in 2010 the age-standardized five-year survival rate for all types and stages of lung cancer combined was only 15 percent for Canada overall, and 12 percent for Alberta.[2] 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 was 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.[3] 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

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

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Tumour Team. Members of the Alberta Provincial Thoracic Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic 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.

This guideline was originally developed in July, 2008. This guideline was revised in September, 2009, June, 2011, January, 2013, March, 2013 and November, 2013.

SEARCH STRATEGY

For the November, 2013 guideline update, the treatment algorithm on page 16 was updated to reflect newly approved provincial coverage of both ALK testing and crizotinib for second line treatment of ALK-positive patients, to describe how this new treatment fits in with overall care for lung cancer patients, and to reflect the specific indications (second line therapy after a failed platinum doublet regimen).

For the January, 2013 guideline update, the working group conducted a search for new or updated practice guidelines published since February 2011 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, and the European Society for Medical Oncology.

Medical journal articles were searched using the EMBASE (2011 to January 2013) and PubMed (February 2011 to January 2013) electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The PubMed search terms were: treatment [MeSH heading] AND stage IV non-small cell lung cancer. The search was limited to the following publication types: humans, adult 19+ years, English, clinical trial, comparative study, controlled clinical trial, guideline, meta-analysis and practice guideline. 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 2011.

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 (except for EGFR-positive patients; see recommendation 6 below). 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, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone.
    - For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) 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 squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used.
9. Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug Review (pCODR) and has also been approved for provincial coverage in Alberta.
10. Testing for ALK mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for second line therapy with crizotinib.
11. 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).[4] 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.[5] 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.[6] 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).[7] 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.[7] 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.[8] 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.[8] Improved response rates in patients treated with a cisplatin-containing triplet regimen were also documented in a recent multicentre phase III trial.[9] 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.[9] Based on the high rates of toxicity and conflicting survival outcomes reported in published studies to date, members of the Alberta Provincial Thoracic Tumour Team do not currently recommended the combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC (recommendation #3).

Non-platinum-based chemotherapy. A phase III RCT by Flotten *et al* in 2012 examined the efficacy of non-platinum CT combinations for first-line treatment of advanced NSCLC in 444 patients.[10] In a comparison of vinorelbine and gemcitabine versus vinorelbine and carboplatin the group found no significant difference in OS rates (6.3 months versus 7.0 months, respectively). In addition, the latter, platinum-containing, group had more grade 3-4 AEs and grade 4 neutropenia.

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;[11-13] 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 non-squamous NSCLC, a slightly higher survival rate when combined with a third-generation agent compared to carboplatin-based regimens.[14-17] 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.[18,19]

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. Early phase clinical trials also report limited efficacy with platinum-based combinations that include the following drugs: ipilimumab[20], custirsen[21], tetrandrine.[22] 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.[23] There were no differences in response rates or median survival among the four regimens, however. This combination was even more effective when combined with rh-endostatin.[24] 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.[25] Teramoto *et al* examined the efficacy of a docetaxel and nedaplatin combination and found this regimen to be well tolerated and active against NSCLC. Larger phase III clinical trials are warranted.[26] Stathapoulos *et al* compared the effectiveness of lipoplatin, a liposomal variant of cisplatin, and paclitaxel against regular cisplatin and paclitaxel. The lipoplatin combination was associated with significantly higher partial response rates although overall survival rates were not affected.[27]

In a 2008 phase III trial, Scagliotti and colleagues randomized chemotherapy-naïve patients with stage IIIB or IV NSCLC to receive either cisplatin/gemcitabine or cisplatin/pemetrexed.[28] 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 non-squamous histology.[6,29,30] 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.[31] Pending confirmatory trials, pemetrexed is only approved for second-line use in Alberta at the present time.

Several studies have been recently published in which experimental drugs combined with standard CT show no difference in outcomes when compared to the current standard. These drugs include bevacizumab[32], custirsen[21], talactoferrin[33], vadimezen[34] and tetrandrine.[22] For many of these studies the authors concluded that additional advanced phase clinical trials are warranted. Until further studies are conducted, however, the current evidence regarding the use of these drugs for advanced NSCLC is limited and, therefore, these drugs are not recommended for use by most clinical practice guidelines.

Socinski *et al* conducted a phase III RCT with 1,052 patients comparing the efficacy of albumin-bound paclitaxel and carboplatin versus solvent-based paclitaxel and carboplatin. The ORR was significantly greater in the albumin-bound cohort (33% versus 25%; p=0.005, respectively). No significant difference in PFS or OS was observed.[35]

Clinical trials published in 2011 and 2012 found several novel drugs that were ineffective in platinum-based combinations for the treatment of advanced NSCLC. A phase II trial with 43 subjects found the combination of gemcitabine and oxaliplatin to show modest activity in advanced NSCLC which they believed warranted further investigation.[36] However, a phase III RCT by Weissman *et al* investigating the same combination was terminated prematurely due to unacceptable toxicities and no observable differences in outcomes when compared to paclitaxel and carboplatin.[37] Other failed combinations include the addition of sorafenib to gemcitabine and cisplatin in a 2012 phase III RCT of 772 patients[38] and the addition of motesanib to carboplatin and paclitaxel in another 2012 phase III RCT of 1090 patients.[39] Hida *et al* published the results of a phase I clinical trial in 2011 assessing the tolerability of vadimezan in combination with paclitaxel and carboplatin[34]. In their 15 subject study they found this combination to be tolerable and urged for further clinical trials. In the same year, however, Lara *et al* published the results of their 1299 subject phase III RCT assessing the clinical activity of vadimezan in combination with the same two chemotherapeutic drugs.[40] The trial was prematurely stopped due to futility. Although the vadimezan-paclitaxel-carboplatin combination was tolerable it was deemed clinically ineffective in the treatment of NSCLC.

It is the consensus of the Alberta Provincial Thoracic 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.[6,18,29,31] 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).[41] 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.[41]

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.

First line chemotherapy for elderly patients (≥65 years) Elderly patients (≥ 65 years) with a PS of 0-1 and no significant comorbidities seem to benefit from combination chemotherapy with a platinum-based doublet.[5,42-46] A phase III RCT by Biesma *et al* in 2011 found that the addition of paclitaxel or gemcitabine to carboplatin did not significantly affect outcome in elderly patients.[47] Some evidence suggests that bevacizumab-based CT may benefit elderly patients in the same way this combination benefits younger patients.[48] A phase II RCT by Spigel *et al* assessed TTP in elderly patients treated with two different triplet CT regimens (pemetrexed/gemcitabine/bevacizumab versus pemetrexed/carboplatin/bevacizumab). They found that the latter regimen was associated with improved TTP and OS.[46] Combinations of erlotinib with gemcitabine or gemcitabine and docetaxel have resulted in mixed results.[49,50] For elderly patients who cannot tolerate a platinum-based combination, the single agents vinorelbine, gemcitabine[51], and docetaxel are all viable options that are associated with improved survival and quality of life when compared to BSC alone (recommendation #5).[5]

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.[52-55] 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.[56] To date, the results of seven 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).[57-63] 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.[57] 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.[58] The most recent phase III trial by Zhou *et al* in 2011 compared erlotinib therapy to a gemcitabine and

carboplatin regimen.[64] The authors found a significant increase in median PFS for the erlotinib group compared to the control CT group (13.6 months versus 4.1 months; HR=0.16; p<0.0001). OS rates were not reported.

Studies published in 2011-2012 examining erlotinib have found it to be highly effective in the treatment of EGFR-mutation positive advanced NSCLC. Recent studies examining erlotinib alone,[64] after failure of first-line platinum-based CT[65] and as a combined regimen with the following: sorafenib[66], gemcitabine[67], bevacizumab[68], and apricoxib[69], have all shown significant increases in PFS, OS or DCR. A phase II randomized trial by Witta *et al* in 2012 evaluated erlotinib with and without entinostat, an isoform selective HDACi, and found that it conferred no benefit over erlotinib monotherapy.[70] Miller *et al* studied the effect of afatinib in patients who had previously failed EGFR-TKIs.[71] This phase II/III double-blind RCT of 585 patients found that although OS rates were not affected, the median PFS of the afatinib group was significantly higher than the placebo group (3.3 months versus 1.1 months; p<0.0001) although it was associated with more AEs. The authors concluded that afatinib could be of use to some patients who fail previous EGFR TKI therapy.[71]

Based on the data published to date, members of the Alberta Provincial Thoracic 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. Gefitinib therapy is currently approved for first-line treatment of advanced NSCLC 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)
Gefitinib Therapy						
Mitsudomi, 2010[61] (West Japan Oncology Group)	CT-naïve, ≤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
			89	cisplatin 80mg/m^2 + docetaxel 60mg/m^2 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
Maemondo, 2010[62] (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^2 q21 days	5.4 HR=0.30; 95% CI 0.22-0.41, p<0.001	23.6 p=0.31
Mok, 2009[63] (IPASS)	CT-naïve, adeno-carcinoma, 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^2 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[59] (First SIGNAL)	CT-naïve, adeno-carcinoma, PS 0-2, never-smoker	IIIB, IV	26*	gefitinib 250mg/day	8.4	30.6
			16*	cisplatin 80mg/m^2 day1, q21 days x 9 cycles + gemcitabine 1250mg/m^2 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
Erlotinib Therapy						
Rosell, 2011[58] (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, 2011[64]	CT-naïve, EGFR-positive	IIIB, IV	82	erlotinib (150mg/d)	13.1	not reported
			72	gemcitabine + carboplatin	4.6 HR=0.16; p<0.0001	
Zhou, 2010[57] (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^2 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.[53,72-76] In Caucasian populations, the rate of EGFR mutations has been reported to range between 7 and 17 percent.[53,56,77,78]

As reported by Rosell *et al.*,[56] 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%).[79] 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.[79] On the basis of this body of literature, and in agreement with recommendations recently made by the American Society of Clinical Oncology,[80] members of the Alberta Provincial Thoracic Tumour Team agree that testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adensquamous) 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.[81] 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 non-squamous 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.[82] 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.[83] 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. A 2012 phase III RCT by Perol *et al* compared gemcitabine or erlotinib maintenance versus observation in 464 patients.[84] All patients had previously received first-line cisplatin and gemcitabine. Upon completion of first-line treatment patients were randomly assigned to observation, gemcitabine on days 1 and 8 of a 3 week cycle at a dosage of 1250mg/m2 or daily erlotinib at a dosage of 150mg/day. The authors found that although there were no differences in OS between the three groups the PFS rates were significantly greater for gemcitabine versus observation (3.8 months vs 1.9 months) and erlotinib versus observation (2.9 months vs 1.9 months). They concluded that gemcitabine continuation maintenance or erlotinib switch maintenance significant reduced disease progression and were well tolerated.

Second-line chemotherapy. The Alberta Provincial Thoracic Tumour Team recommends therapy with single-agent docetaxel or erlotinib for patients with squamous cell carcinoma 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.[85]

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^2 every three weeks as a standard therapy in the second-line setting.[86,87] In the TAX317 trial, treatment with 75 mg/m^2 docetaxel was associated with longer time to disease progression, longer median survival, and a better one-year survival rate when compared to BSC.[86] 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.[88] In the TAX320 trial, overall survival was not significantly different in patients treated with 75 mg/m^2 docetaxel, 100 mg/m^2 docetaxel, vinorelbine, or ifosfamide. However, the one-year survival rate was significantly higher for patients treated with 75 mg/m^2 docetaxel.[87] 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.[89-94] 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).[95] 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.[96] Pemetrexed was associated with significantly fewer side effects when compared with docetaxel, particularly grade 3-4 neutropenia, febrile neutropenia, neutropenia with infection, and alopecia.[96] Patients treated with pemetrexed in this trial

required supplementation with vitamin B_{12} (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).[97] 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.[98] 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. A phase I trial published in 2011 examined the feasibility and safety of pemetrexed in combination with everolimus as a second-line treatment for advanced NSCLC.[99] They found this regiment to be feasible and acceptably toxic with most frequent grade 3-4 AEs being neutropenia, dyspnea and thrombocytopaenia. They recommended an everolimus starting dose of 5 mg/day or 50 mg/week in future clinical trials.

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.[100] 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).[100] 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.[100,101] Preliminary findings from the multicentre, open-label phase III TITAN trial were also recently published.[102] 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%).[102] Recent studies have looked how gemcitabine followed by erlotinib at progression differs from the reverse treatment as a second-line therapy. Although both strategies were feasible the authors found that they had only modest efficacy, with median OS rates of 4.4 months for the former strategy and 3.9 months for the latter (p=NSD).[103]

Other smaller phase I or II studies have examined the roles of talactoferrin (TLF), pralatrexate and mitomycin as second-line treatments. Parikh *et al* conducted a double-blind RCT with 100 patients to investigate the activity of oral TLF and BSC compared to placebo and BSC.[104] In the experimental group, median OS increased by 65% (3.7 months to 6.1 months). Similar trends appeared to exist for PFS and DCR. Toxicity was generally tolerable. In 2011 Azzoli *et al* evaluated the safety of pralatrexate and vitamin supplementation in a phase I clinical trial with 39 patients.[105] This combination resulted in a 10% ORR with common grade 3-4 AEs including mucositis and fatigue. Finally, another 2011 study by Stenger *et al* examined the efficacy of mitomycin in combination with either vinorelbine or cisplatin (depending on

whether cisplatin was used as a first-line treatment) with 14 patients.[106] Mitomycin was prescribed at a dose of 8 mg/m2. The authors found that 1 patient had a PR and 6 had SD. The median TTP was 2.3 months and the median OS was 4.6 months. Four patients experienced grade 3-4 leukocytopaenia and 4 experienced grade 3-4 neutropenia. The authors concluded that further investigations of mitomycin combinations are warranted.

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.[107] 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).[107] 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.[108,109] 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.[108] 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.[109]

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.[110] 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.[111] 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.

Treatments for ALK-Positive Rearrangements

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.[112] ALK translocations have been noted in never-smokers, patients with adenocarcinoma and younger patients.[113] Patients with ALK translocations appear to be less sensitive to EGFR inhibitors and standard CT than those without.[114]

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.[115] Lee *et al* conducted a restrospective analysis of 1,166 patients to investigate outcome rates of patients with advanced NSCLC who were managed in the pre-ALK inhibitor era.[116] OS rates were compared across three groups: patients who were ALK-positive, patients who were EGFR-positive and patients who were ALK and EGFR wild types. The median OS rates in these groups were 12.2 months, 29.6 months and 19.3 months, respectively. Median PFS rates were similar in all groups although PFS rates for patients who received EGFR TKIs was shorter in ALK-positive patients compared to other groups. In the pre ALK-inhibitor era, therefore, ALK-positive patients experienced shorter survival on par with wild type patients. In addition, ALK-positive patients were more resistant to EGFR TKI treatment than wild type patients..

Recently, a phase II clinical trial by Kim *et al*[113] and a phase III clinical trial by Shaw *et al*[117] investigated the efficacy and safety of crizotinib; building off the results from an earlier phase I, single-arm clinical trial by Camidge et al.[118] In the study by Kim *et al*, published as an abstract at the ASCO 2012 conference, patients with ALK-positive NSCLC were given 250mg BID crizotinib in three-week cycles. An ORR of 53% and 12-week DCR of 85% was observed with a median PFS of 8.5 months. Significant improvements in post-treatment pain, cough, and global QoL were reported. In the phase III clinical trial conducted by Shaw *et al*, also published as an abstract, this time at the ESMO 2012 conference, crizotinib was compared to standard CT for advanced NSCLC. Like before, 250mg BID crizotinib was administered to 173 patients with another 174 patients receiving either 500mg/m^2 pemetrexed (57%) or 75mg/m^2 docetaxel (41%). Crizotinib prolonged PFS to median of 7.7 months from 3 months for those treated with standard CT (HR 0.49, CI 0.37-0.64, p<0.0001). The ORR was significantly higher in those treated with crizotinib (65% versus 20%; p<0.0001). The OS data were still not mature. As there was significant crossover from the standard CT group to the crizotinib group it is possible that OS results may not significantly differ. That said, however, the authors believe crizotinib should be the new standard of care for individuals with ALK-positive advanced NSCLC. As a result of these, and other promising results[119], the US FDA have approved crizotinib for patients with ALK-positive advanced or metastatic NSCLC.

The results of these early trials 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. Indeed, guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology now recommend ALK gene rearrangement testing to better treat those patients with advanced NSCLC who are ALK-positive.

Axitinib

Axitinib is a TKI that inhibits multiple targets including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and cKIT. Two early phase studies, published in 2009 and 2012, have examined the efficacy and safety of axitinib in the treatment of advanced NSCLC.[120,121] Schiller *et al* studied the efficacy and safety of single-agent axitinib in a phase II clinical trial with 32 patients. They observed PR and DCR rates of 9% and 41%, respectively. The median PFS was 4.9 months and median OS was 14.8 months. One-year OS percentages were 57% for those patients who received prior therapy for metastatic disease and 78% for those who had not received prior therapy.[120] In a 2012 phase I clinical trial, Kozloff *et al* evaluated the efficacy of axitinib in combination with a paclitaxel-carboplatin combination or gemcitabine-cisplatin combination. Once a maximum tolerated dose was determined an expanded cohort was enrolled to receive an axitinib-paclitaxel-carboplatin regimen. Two patients (of the 49) experienced dose limiting toxicities. The authors concluded that both regimes tested were well tolerated.[121] Further studies on axitinib are required to determine its role in treating advanced NSCLC.

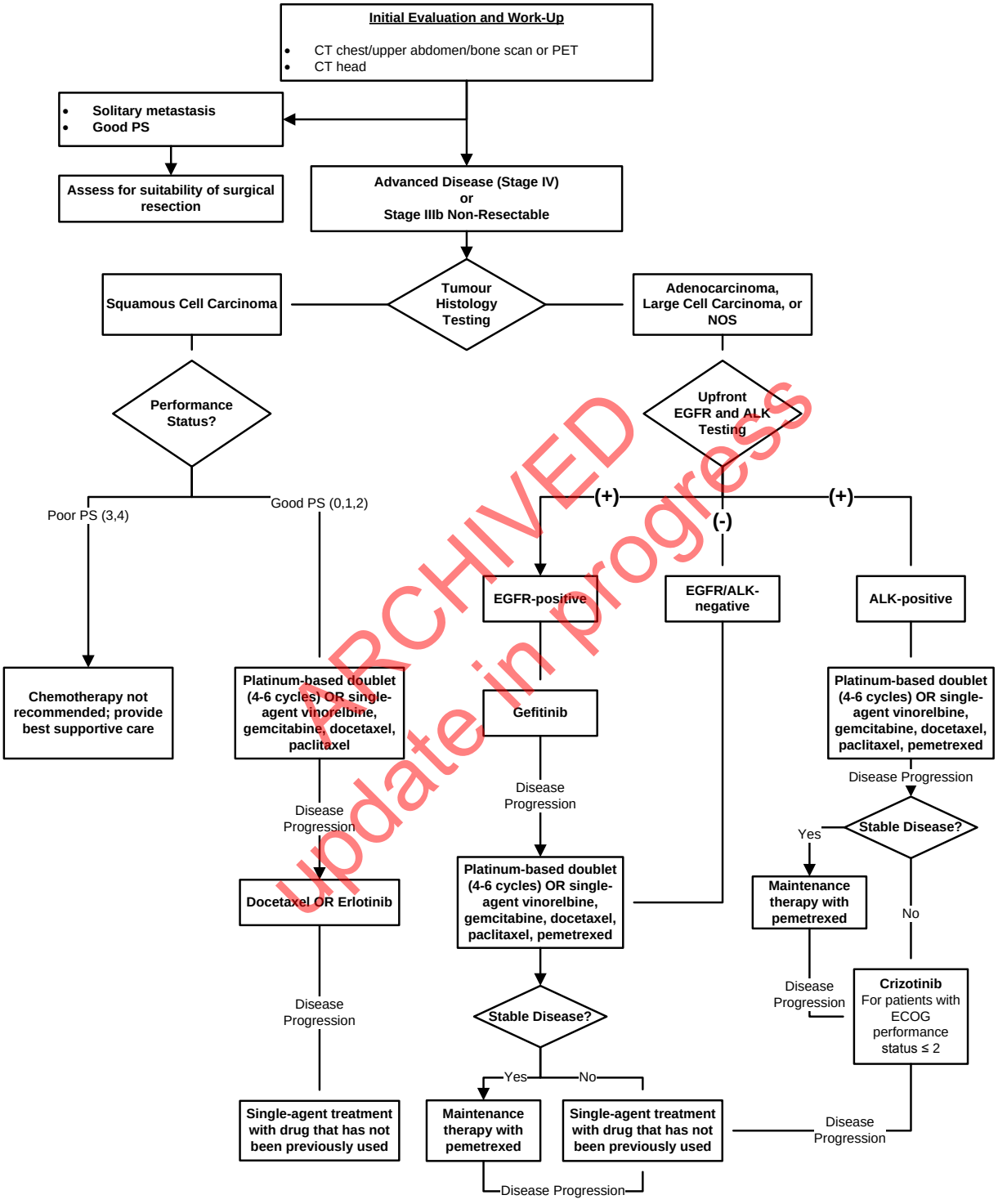
Palliative Radiotherapy

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 #11).

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.[122] 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.[77] 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.

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.[123] 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.[124] However, the Alberta Provincial Thoracic 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.[125] 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).[125] For a detailed review and treatment recommendations regarding palliative radiotherapy, please refer to the Palliative Radiotherapy Clinical Practice Guideline.

TREATMENT ALGORITHM



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
DCR	Disease Control Rate
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EML4	Echinoderm Microtubule-Associated Protein-Like 4 Gene
Gy	Gray
HDACi	Histone Deacetylase Inhibitors
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
OS	Overall Survival
PDGFR	Platelet-Derived Growth Factor Receptor
PET	Positron Emission Tomography
PFS	Progression Free Survival
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
TTP	Time To Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
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, CancerControl.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. 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 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 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.

REFERENCES

1. Canadian Cancer Society. Canadian Cancer Statistics 2012. 2012; http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2012---English.pdf. Accessed Feb 20, 2013.
2. Committee CCSsS. Canadian Cancer Statistics 2009. 2009; 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 March 11, 2011.
3. Demeter SJ, Jacobs P, Chmielowiec C, et al. The cost of lung cancer in Alberta. *Can Respir J.* Mar 2007;14(2):81-86.
4. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest.* Jul 2009;136(1):260-271.
5. Socinski MA, Crowell R, Hensing TE, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest.* Sep 2007;132(3 Suppl):277S-289S.
6. D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* May 2010;21 Suppl 5:v116-119.
7. Delbaldo C, Michiels S, Rolland E, et al. Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. *Cochrane Database Syst Rev.* 2007;4(CD004569).
8. Paccagnella A, Oniga F, Bearz A, et al. Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non-small-cell lung cancer: results of a phase II-III study. *J Clin Oncol.* Feb 1 2006;24(4):681-687.
9. Comella P, Filippelli G, De Cataldis G, et al. Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: a phase III randomised trial of the Southern Italy Cooperative Oncology Group (SICOG 0101). *Ann Oncol.* Feb 2007;18(2):324-330.
10. Flotten O, Gronberg BH, Bremnes R, et al. Vinorelbine and gemcitabine vs vinorelbine and carboplatin as first-line treatment of advanced NSCLC. A phase III randomised controlled trial by the Norwegian Lung Cancer Study Group. *Br J Cancer.* Jul 24 2012;107(3):442-447.
11. Pujol JL, Barlesi F, Daures JP. Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. *Lung Cancer.* Mar 2006;51(3):335-345.
12. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd 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.* May 1 2005;23(13):2926-2936.
13. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ.* Oct 7 1995;311(7010):899-909.
14. 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.* Sep 2007;57(3):348-358.
15. Ardizzoni A, Boni L, Tiseo 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.* Jun 6 2007;99(11):847-857.
16. 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.* Jan 2008;59(1):1-11.
17. 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.* Oct 1 2004;22(19):3852-3859.
18. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol.* Dec 20 2009;27(36):6251-6266.

19. Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. *Oncologist.* 2008;13 Suppl 1:5-13.

20. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol.* Jun 10 2012;30(17):2046-2054.

21. Laskin JJ, Nicholas G, Lee C, et al. Phase I/II trial of custirsen (OGX-011), an inhibitor of clusterin, in combination with a gemcitabine and platinum regimen in patients with previously untreated advanced non-small cell lung cancer. *J Thorac Oncol.* Mar 2012;7(3):579-586.

22. Liu W, Ying C, Wang Q, et al. Tetrandrine combined with gemcitabine and cisplatin for patients with advanced non-small cell lung cancer improve efficacy. *International Journal of Biomedical Sciences.* 2012;8(1).

23. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* Jan 10 2002;346(2):92-98.

24. Zhao X, Mei K, Cai X, et al. A randomized phase II study of recombinant human endostatin plus gemcitabine/cisplatin compared with gemcitabine/cisplatin alone as first-line therapy in advanced non-small-cell lung cancer. *Invest New Drugs.* Jun 2012;30(3):1144-1149.

25. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol.* Feb 2007;18(2):317-323.

26. Teramoto K, Asada Y, Ozaki Y, et al. A phase II study of docetaxel plus nedaplatin in patients with metastatic non-small-cell lung cancer. *Cancer Chemother Pharmacol.* Oct 2012;70(4):531-537.

27. Stathopoulos GP, Antoniou D, Dimitroulis J, Stathopoulos J, Marosis K, Michalopoulou P. Comparison of liposomal cisplatin versus cisplatin in non-squamous cell non-small-cell lung cancer. *Cancer Chemother Pharmacol.* Oct 2011;68(4):945-950.

28. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* Jul 20 2008;26(21):3543-3551.

29. Network NCC. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 3.2011. 2011; www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 11, 2011.

30. Agency BCC. BCCA protocol summary for first-line treatment of advanced non-small cell lung cancer with platinum and pemetrexed. 2011; www.bccancer.bc.ca/NR/rdonlyres/5743F797-D252-42DB-B689-339C079C904B/49416/ULUAVPP_Protocol_1Feb2011.pdf. Accessed March 22, 2011.

31. Goffin J LC, 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, Version 2.2010. 2011; http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=45735. Accessed March 22, 2011.

32. Leon L, Vazquez S, Gracia JM, et al. First-line bevacizumab, cisplatin and vinorelbine plus maintenance bevacizumab in advanced non-squamous non-small cell lung cancer chemo-naive patients. *Expert Opin Pharmacother.* Jul 2012;13(10):1389-1396.

33. Digumarti R, Wang Y, Raman G, et al. A randomized, double-blind, placebo-controlled, phase II study of oral talactoferrin in combination with carboplatin and paclitaxel in previously untreated locally advanced or metastatic non-small cell lung cancer. *J Thorac Oncol.* Jun 2011;6(6):1098-1103.

34. Hida T, Tamiya M, Nishio M, et al. Phase I study of intravenous ASA404 (vadimezan) administered in combination with paclitaxel and carboplatin in Japanese patients with non-small cell lung cancer. *Cancer Sci.* Apr 2011;102(4):845-851.

35. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol.* Jun 10 2012;30(17):2055-2062.

36. Mitchell PL, Broad A, Rosenthal MA, et al. Randomized phase 2 sequencing and pharmacokinetic study of gemcitabine and oxaliplatin in advanced non-small cell lung cancer. *Asia Pac J Clin Oncol.* Dec 2011;7(4):376-384.

37. Weissman CH, Reynolds CH, Neubauer MA, Pritchard S, Kobina S, Asmar L. A phase III randomized trial of gemcitabine-oxaliplatin versus carboplatin-paclitaxel as first-line therapy in patients with advanced non-small cell lung cancer. *J Thorac Oncol.* Feb 2011;6(2):358-364.

38. Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. *J Clin Oncol.* Sep 1 2012;30(25):3084-3092.

39. Scagliotti GV, Vynnychenko I, Park K, et al. International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer: MONET1. *J Clin Oncol.* Aug 10 2012;30(23):2829-2836.

40. Lara PN, Jr., Douillard JY, Nakagawa K, et al. Randomized phase III placebo-controlled trial of carboplatin and paclitaxel with or without the vascular disrupting agent vadimezan (ASA404) in advanced non-small-cell lung cancer. *J Clin Oncol.* Aug 1 2011;29(22):2965-2971.

41. Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. *J Thorac Oncol.* Sep 2007;2(9):845-853.

42. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst.* Feb 6 2002;94(3):173-181.

43. Belani CP, Fossella F. Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). *Cancer.* Dec 15 2005;104(12):2766-2774.

44. Hensing TA, Peterman AH, Schell MJ, Lee JH, Socinski MA. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, Stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. *Cancer.* Aug 15 2003;98(4):779-788.

45. Ansari RH, Socinski MA, Edelman MJ, et al. A retrospective analysis of outcomes by age in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel vs. paclitaxel plus carboplatin for advanced non-small cell lung cancer. *Crit Rev Oncol Hematol.* May 2011;78(2):162-171.

46. Spigel DR, Hainsworth JD, Shipley DL, et al. A randomized phase II trial of pemetrexed/gemcitabine/bevacizumab or pemetrexed/carboplatin/bevacizumab in the first-line treatment of elderly patients with advanced non-small cell lung cancer. *J Thorac Oncol.* Jan 2012;7(1):196-202.

47. Biesma B, Wymenga AN, Vincent A, et al. Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. *Ann Oncol.* Jul 2011;22(7):1520-1527.

48. Laskin J, Crino L, Felip E, et al. Safety and efficacy of first-line bevacizumab plus chemotherapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer: safety of avastin in lung trial (MO19390). *J Thorac Oncol.* Jan 2012;7(1):203-211.

49. LeCaer H, Barlesi F, Corre R, et al. A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study). *Br J Cancer.* Oct 11 2011;105(8):1123-1130.

50. Stinchcombe TE, Peterman AH, Lee CB, et al. A randomized phase II trial of first-line treatment with gemcitabine, erlotinib, or gemcitabine and erlotinib in elderly patients (age >/=70 years) with stage IIIB/IV non-small cell lung cancer. *J Thorac Oncol.* Sep 2011;6(9):1569-1577.

51. Baek JH, Kim H, Ahn JJ, et al. Prospective phase II trial of a combination of gemcitabine and UFT as first-line treatment in elderly patients with advanced non-small cell lung cancer. *Lung Cancer.* Jun 2012;76(3):368-372.

52. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* May 20 2004;350(21):2129-2139.

53. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* Jun 4 2004;304(5676):1497-1500.

54. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* Sep 7 2004;101(36):13306-13311.

55. Huang SF, Liu HP, Li LH, et al. High frequency of epidermal growth factor receptor mutations with complex patterns in non-small cell lung cancers related to gefitinib responsiveness in Taiwan. *Clin Cancer Res.* Dec 15 2004;10(24):8195-8203.

56. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med.* Sep 3 2009;361(10):958-967.

57. Zhou C, Wu YL, Chen G, Feng J, Liu X, Wang C. Efficacy results from the randomised phase III OPTIMAL (CTOG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced non-small cell lung cancer (NSCLC) patients (PTS) with EGFR activating mutations. . In: Oncol A, ed. *ESMO 2010 Meeting.* Vol 212010.

58. Rosell R, Gervais R, Vergnenegre A, Massuti B, Felip E, Cardenal F. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial. . In: Oncol JC, ed. *ASCO 2011 Annual Meeting.* Vol 292011.

59. Lee JS, Park K, Kim SW, Lee DH, Kim HT, Han JY. A randomized phase III study of gefitinib (IRESSA™) versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung. . In: Oncol JT, ed. *13th World Conference on Lung Cancer.* Vol 42009.

60. Yang CH, Fukuoka M, Mok T, Wu YL, Thongprasert S, Saijo N. Final overall survival (OS) results from a phase III, randomised, open-label, first-line study of gefitinib (G) v carboplatin/paclitaxel (C/P) in clinically selected patients with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS). . In: Oncol A, ed. *ESMO 2010 Meeting.* Vol 212010.

61. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* Feb 2010;11(2):121-128.
62. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med.* Jun 24 2010;362(25):2380-2388.
63. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* Sep 3 2009;361(10):947-957.
64. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* Aug 2011;12(8):735-742.
65. Kowalski DM, Krzakowski M, Ramlau R, Jaskiewicz P, Janowicz-Zebrowska A. Erlotinib in salvage treatment of patients with advanced non-small cell lung cancer: results of an expanded access programme in Poland. *Wspolczesna Onkol.* 2012;16(2):170-175.
66. Gridelli C, Morgillo F, Favaretto A, et al. Sorafenib in combination with erlotinib or with gemcitabine in elderly patients with advanced non-small-cell lung cancer: a randomized phase II study. *Ann Oncol.* Jul 2011;22(7):1528-1534.
67. Michael M, Pavlakis N, Clingan P, De Boer R, Johnston M, Clarke S. A multi-centre randomized, open-label phase II trial of continuous erlotinib plus gemcitabine or gemcitabine as first-line therapy in ECOG PS2 patients with advanced non-small cell lung cancer. *Oncol Rep.* Sep 2012;28(3):763-767.
68. Dingemans AM, de Langen AJ, van den Boogaart V, et al. First-line erlotinib and bevacizumab in patients with locally advanced and/or metastatic non-small-cell lung cancer: a phase II study including molecular imaging. *Ann Oncol.* Mar 2011;22(3):559-566.
69. Reckamp K, Gitlitz B, Chen LC, et al. Biomarker-based phase I dose-escalation, pharmacokinetic, and pharmacodynamic study of oral apricoxib in combination with erlotinib in advanced nonsmall cell lung cancer. *Cancer.* Feb 15 2011;117(4):809-818.
70. Witta SE, Jotte RM, Konduri K, et al. Randomized phase II trial of erlotinib with and without entinostat in patients with advanced non-small-cell lung cancer who progressed on prior chemotherapy. *J Clin Oncol.* Jun 20 2012;30(18):2248-2255.
71. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol.* May 2012;13(5):528-538.
72. Satouchi M, Negoro S, Funada Y, et al. Predictive factors associated with prolonged survival in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib. *Br J Cancer.* Apr 23 2007;96(8):1191-1196.
73. Tokumo M, Toyooka S, Kiura K, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res.* Feb 1 2005;11(3):1167-1173.
74. Tanaka T, Matsuoka M, Sutani A, et al. Frequency of and variables associated with the EGFR mutation and its subtypes. *Int J Cancer.* Feb 1 2010;126(3):651-655.
75. Sasaki H, Shimizu S, Endo K, et al. EGFR and erbB2 mutation status in Japanese lung cancer patients. *Int J Cancer.* Jan 1 2006;118(1):180-184.
76. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst.* Mar 2 2005;97(5):339-346.
77. Savic S, Tapia C, Grilli B, et al. Comprehensive epidermal growth factor receptor gene analysis from cytological specimens of non-small-cell lung cancers. *Br J Cancer.* Jan 15 2008;98(1):154-160.
78. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst.* May 4 2005;97(9):643-655.
79. D'Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J Clin Oncol.* May 20 2011;29(15):2066-2070.
80. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *J Clin Oncol.* May 20 2011;29(15):2121-2127.
81. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet.* Oct 24 2009;374(9699):1432-1440.
82. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* Jun 2010;11(6):521-529.
83. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol.* Feb 1 2009;27(4):591-598.

84. Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol.* Oct 1 2012;30(28):3516-3524.
85. Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist.* 2008;13 Suppl 1:28-36.
86. Shepherd FA, Dancey J, Ramlau R, 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.* May 2000;18(10):2095-2103.
87. Fossella FV, DeVore R, Kerr RN, 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.* Jun 2000;18(12):2354-2362.
88. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. *Lung Cancer.* Feb 2004;43(2):183-194.
89. Gridelli C, Gallo C, Di Maio M, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. *Br J Cancer.* Dec 13 2004;91(12):1996-2004.
90. Camps C, Massuti B, Jimenez A, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. *Ann Oncol.* Mar 2006;17(3):467-472.
91. Chen YM, Shih JF, Perng RP, Tsai CM, Whang-Peng J. A randomized trial of different docetaxel schedules in non-small cell lung cancer patients who failed previous platinum-based chemotherapy. *Chest.* Apr 2006;129(4):1031-1038.
92. Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol.* Nov 20 2005;23(33):8389-8395.
93. Gervais R, Ducolone A, Breton JL, et al. Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* Jan 2005;16(1):90-96.
94. Lai CL, Tsai CM, Chiu CH, et al. Phase II randomized trial of tri-weekly versus days 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. *Jpn J Clin Oncol.* Dec 2005;35(12):700-706.
95. Di Maio M, Perrone F, Chiodini P, et al. Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol.* Apr 10 2007;25(11):1377-1382.
96. Hanna N, Shepherd FA, Fossella FV, 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.* May 1 2004;22(9):1589-1597.
97. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist.* Mar 2009;14(3):253-263.
98. Weiss GJ, Langer C, Rosell R, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* Sep 20 2006;24(27):4405-4411.
99. Vansteenkiste J, Solomon B, Boyer M, et al. Everolimus in combination with pemetrexed in patients with advanced non-small cell lung cancer previously treated with chemotherapy: a phase I study using a novel, adaptive Bayesian dose-escalation model. *J Thorac Oncol.* Dec 2011;6(12):2120-2129.
100. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* Jul 14 2005;353(2):123-132.
101. Florescu M, Hasan B, Seymour L, Ding K, Shepherd FA. A clinical prognostic index for patients treated with erlotinib in National Cancer Institute of Canada Clinical Trials Group study BR.21. *J Thorac Oncol.* Jun 2008;3(6):590-598.
102. Ciuleanu T, Stelmakh L, Cicenas S, Esteban E. Erlotinib versus docetaxel or pemetrexed as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) and poor prognosis: efficacy and safety results from the phase III TITAN study. . In: Oncol JT, ed. Vol 52010.
103. LeCaer H, Greillier L, Corre R, et al. A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study). *Lung Cancer.* Jul 2012;77(1):97-103.
104. Parikh PM, Vaid A, Advani SH, et al. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. *J Clin Oncol.* Nov 1 2011;29(31):4129-4136.
105. Azzoli CG, Patel JD, Krug LM, et al. Pralatrexate with vitamin supplementation in patients with previously treated, advanced non-small cell lung cancer: safety and efficacy in a phase 1 trial. *J Thorac Oncol.* Nov 2011;6(11):1915-1922.
106. Stenger L, Tomala C, Pietsch M, et al. Mitomycin C in combination with vinorelbine or cisplatin and erythropoietin in pretreated patients with in field relapse after radiation therapy of non-small cell lung cancer: a phase II trial of the AIO. *Magazine of European Medical Oncology.* 2011;4(1):31-37.

107. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* Dec 14 2006;355(24):2542-2550.
108. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol.* Mar 10 2009;27(8):1227-1234.
109. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol.* Sep 2010;21(9):1804-1809.
110. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet.* May 2 2009;373(9674):1525-1531.
111. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. *J Clin Oncol.* Feb 20 2010;28(6):911-917.
112. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature.* Aug 2 2007;448(7153):561-566.
113. Kim DW, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Paper presented at: 2012 Annual Meeting of the American Society of Clinical Oncology2012.
114. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. *CA Cancer J Clin.* Mar-Apr 2011;61(2):91-112.
115. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* Oct 28 2010;363(18):1693-1703.
116. Lee JK, Park HS, Kim DW, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. *Cancer.* Jul 15 2012;118(14):3579-3586.
117. Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 20122012.
118. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol.* Oct 2012;13(10):1011-1019.
119. Kimura H, Nakajima T, Takeuchi K, et al. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. *Lung Cancer.* 2012;75(1):66-72.
120. Schiller JH, Larson T, Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. *J Clin Oncol.* Aug 10 2009;27(23):3836-3841.
121. Kozloff MF, Martin LP, Krzakowski M, et al. Phase I trial of axitinib combined with platinum doublets in patients with advanced non-small cell lung cancer and other solid tumours. *Br J Cancer.* Oct 9 2012;107(8):1277-1285.
122. Lester JF, Macbeth FR, Toy E, Coles B. Palliative radiotherapy regimens for non-small cell lung cancer (Article CD002143). *Cochrane Database Syst Rev* 2006(4).
123. Okawara G, Mackay JA, Evans WK, Ung YC, Group LCDS. Management of unresected stage III non-small cell lung cancer: a clinical practice guideline. Evidence Based Series #7-3, Version 2.2005. . 2005; http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14206 Accessed March 22, 2011.
124. Bezjak A, Dixon P, Brundage M, 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.* Nov 1 2002;54(3):719-728.
125. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol.* Aug 20 2008;26(24):4001-4011.