



Evidence-Based Series #7-9 Version 2

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

**Use of the Epidermal Growth Factor Receptor Inhibitors
Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib
or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A
Clinical Practice Guideline**

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung, and the Lung Disease Site Group (DSG)

Report Date: May 8, 2014

An assessment conducted in December 2016 deferred the review of Evidence-based Series (EBS) 7-9 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Evidence-Based Series #7-9 v2 is comprised of 3 sections:

Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base
Section 3:	Development Methods, Recommendations Development, and External Review Process

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Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2006 May;1(4):367-76.

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Use of the Epidermal Growth Factor Receptor Inhibitors
Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib,
Dacomitinib or Icotinib in the Treatment of Non-Small-Cell
Lung Cancer: A Clinical Practice Guideline

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung, and the Lung DSG

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2006	1966 to November 2005	Full Report	Peer review publication. Web publication.	Not Applicable
Version 2 2013	2005 to March 2014	New data and old data integrated in new Full Report	Updated web publication.	Not Applicable

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Use of the Epidermal Growth Factor Receptor Inhibitors
Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib,
Dacomitinib or Icotinib in the Treatment of Non-Small-Cell
Lung Cancer: A Clinical Practice Guideline
Guideline Recommendations

P.M. Ellis, N. Coakley, R. Feld, S. Kuruvilla, Y.C. Ung, and the Lung DSG

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Report Date: May 8, 2014

QUESTIONS

1. In patients with advanced non-small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)?
2. In patients with advanced NSCLC who have progressed on platinum-based chemotherapy, does subsequent therapy with EGFR inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib improve overall survival or PFS? Is there a preferred sequence for second-line therapy with an EGFR inhibitor or chemotherapy?
3. In patients with advanced stage IIIB or IV NSCLC who have received initial first-line platinum-based chemotherapy, does maintenance therapy with erlotinib, gefitinib, afatinib, dacomitinib or icotinib improve overall survival or PFS?
4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?

TARGET POPULATION

This practice guideline applies to adult patients with advanced (stage IIIB or IV) non-small-cell lung cancer.

INTENDED USERS

This guideline is targeted for clinicians involved in the delivery of systemic treatment for cancer patients.

RECOMMENDATIONS AND KEY EVIDENCE

Recommendation 1a

First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients.

The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations.

Key Evidence

Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients (1-26).

Recommendation 1b

In patients with EGFR mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib or afatinib is the preferred treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer PFS and improved quality of life.

Qualifying Statement

There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative.

Key Evidence

Seven randomized trials and two meta-analyses comprised the evidence base. The trials and meta-analyses based on data from these trials showed that PFS was prolonged in molecularly selected patients when an EGFR was used as first-line treatment (27-33).

- Six trials were included in the initial meta-analysis that showed a hazard ratio (HR) of 0.35 (95% confidence interval (CI), 0.28-0.45; $p < 0.00001$) (27-30,32,33).
- A second meta-analysis done on PFS that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.38 (95% CI, 0.31-0.44; $p < 0.00001$) (20,21,28-30,32-34).
- All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy (28-34).

Recommendation 2

In patients well enough to consider second-line chemotherapy, an EGFR TKI can be recommended as second- or third-line therapy.

There is insufficient evidence to recommend the use of a second EGFR TKI, such as afatinib, in patients whose disease has progressed following chemotherapy and gefitinib or erlotinib, as available data does not demonstrate any improvement in overall survival

Qualifying Statements

There are data to support the use of an EGFR TKI in patients who have progressed on platinum-based chemotherapy. Erlotinib is known to improve overall survival and quality of life when used as second- or third-line therapy, in comparison to best supportive care.

However, available data would suggest that second-line therapy with either chemotherapy or an EGFR TKI results in similar PFS and overall survival. Available evidence would support the use of either erlotinib or gefitinib in this situation.

Data from a randomized phase II trial suggests improved PFS for dacomitinib versus (vs) erlotinib, but these data require confirmation in a phase III trial.

The Lux Lung 1 study failed to meet its primary outcome of improved overall survival. However, the study showed improved PFS for patients randomized to afatinib and was associated with improvements in lung cancer symptoms.

Key Evidence

- Three studies examined an EGFR inhibitor as a second-line treatment against a placebo and best supportive care (35-37). One study reported on the use of erlotinib and showed a significant improvement in PFS ($p=0.001$) and overall survival ($p=0.001$) (35). The other two studies evaluated gefitinib, with one study finding significant results for response rate ($p<0.0001$) (37) and the other for PFS ($p=0.002$) (36).
- A meta-analysis done on seven second-line studies showed no improvement with EGFR TKIs vs chemotherapy for progression-free survival (HR, 0.99; 95% CI 0.86-1.12, $p=0.67$) and overall survival (HR, 1.02; 95% CI, 0.95-1.09, $p=0.56$) (38-44)
- One phase II study that compared erlotinib to dacomitinib (45) showed significant results for dacomitinib for response rate ($p=0.011$) and for PFS ($p=0.012$).
- The Lung Lux 1 study examined the use of afatinib in the third- and fourth-line setting against a placebo. This study showed improved PFS (HR, 0.38; 95% CI, 0.31-0.48, $p<0.0001$) but no difference in overall survival (HR, 1.08; 95% CI, 0.86-1.35, $p=0.74$) (46).

Recommendation 3

An EGFR TKI is recommended as an option for maintenance therapy in patients who have not progressed after four cycles of a platinum-doublet chemotherapy. No recommendation can be made with respect to the choice of gefitinib or erlotinib.

Qualifying Statements

- Trials have evaluated both erlotinib and gefitinib, but no trials directly compare these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the overall survival advantage is modest for both agents.
- There are competing strategies of maintenance chemotherapy without an EGFR TKI, such as pemetrexed, that are not addressed in this guideline. The recommendation

for TKI above should not be taken as excluding these other strategies as reasonable options; as this evidence was not reviewed, no statement can be made for or against these other strategies. The Lung Disease Site Group (DSG) plans to develop a separate guideline on maintenance therapy as soon as possible.

- This recommendation applies to both EGFR mutation positive and wild-type patients.

Key Evidence

Six studies evaluated the use of an EGFR inhibitor in the maintenance setting (47-52).

- Two of the trials reported a statistically significant survival benefit with erlotinib: one for response rate ($p=0.0006$) when compared to placebo (47) and one for progression-free survival when combined with bevacizumab against bevacizumab alone ($p<0.001$) (51).
- One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs 7%) and 9.1 months vs 8.3 months for overall survival (50).
- Two trials evaluating gefitinib found a statistically significant benefit for PFS in the maintenance setting, $p<0.001$ when combined with chemotherapy and against chemotherapy (48) and $p<0.0001$ compared to a placebo (49).
- Another trial evaluated gefitinib and showed a higher response rate, but this was not significant ($p=0.369$) (52).

Recommendation 4

The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity.

Key Evidence

- Two randomized phase II trials (53-54), each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients) (53).
- One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib (45).
- One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs 8%) (54).

RELATED GUIDELINES

A previous version of this guideline is contained in: Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. *J Thorac Oncol.* 2006;1(4):367-76.

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