Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series #7-9 Version 2 BEING UPDATED

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 2017 indicated that Evidence-based Series (EBS) 7-9 Version 2 will be UPDATED. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 7-9 v2 is comprised of 3 sections and is available on the CCO Lung Cancer page:

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

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC; Lung Disease Site Group. 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. Toronto (ON): Cancer Care Ontario; 2014 Apr 23 [Being Updated 2017 Dec]. Program in Evidence-based Care Evidence-based Series No.: 7-9 Version 2 BEING UPDATED.

Journal Citations (Vancouver Style): Ellis PM, Coakley N, Feld R, Kuruvilla S, Ung YC. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review. Curr Oncol. 2015 Jun;22(3):e183-215.

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.

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 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

Table of Contents

Evidence-Based Series #7-9 Version 2: Section 1

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 Guideline Recommendations

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

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

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.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Contact Information

For further information about this report, please contact:
Dr. Yee C. Ung, Co-Chair, Lung Cancer Disease Site Group, Odette Cancer Centre,
2075 Bayview Avenue, Toronto, ON M4N 3M5; Tel: (416) 480-4951; Fax: (416) 480-6002.
or
Dr. Peter Ellis, Co-Chair, Lung Cancer Disease Site Group, McMaster University and
Juravinski Cancer Centre, 699 Concession Street, Hamilton ON L8V 5C2;
Tel: (905) 387-9711 ext. 64609; Fax (905) 575-6323.

For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol. 2007;25(12):1545-52.
2. Gridelli C, Ciardiello F, Gallo C, Feld R, Butts C, Gebbia V, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: The TORCH Randomized Trial. J Clin Oncol. 2012;30(24):3002-11.
3. Chen Y-M, Tsai C-M, Fan W-C, Shih J-F, Liu S-H, Wu C-H, et al. Phase II randomized trial of erlotinib or vinorelbine in chemonaive, advanced, non-small cell lung cancer patients aged 70 years or older. J Thorac Oncol. 2012;7(2):412-8.
4. Crino L, Cappuzzo F, Zatloukal P, Reck M, Pesek M, Thompson JC, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. J Clin Oncol. 2008;26(26):4253-60.
5. Goss G, Ferry D, Wierzbicki R, Laurie SA, Thompson J, Biesma B, et al. Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. J Clin Oncol. 2009;27(13):2253-60.
6. Gridelli C, Morgillo F, Favaretto A, de Marinis F, Chella A, Cerea G, 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. 2011;22(7):1528-34.
7. LeCaer H, Barlesi F, Corre R, Jullian H, Bota S, Falchero L, 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. 2011;105(8):1123-30.
8. Lilenbaum R, Axelrod R, Thomas S, Dowlati A, Seigel L, Albert D, et al. Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. J Clin Oncol. 2008;26(6):863-9.
9. Mok TSK, Wu Y-L, Yu C-J, Zhou C, Chen Y-M, Zhang L, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(30):5080-7.
10. Morere JF, Brechot JM, Westeel V, Gounant V, Lebeau B, Vaylet F, et al. Randomized phase II trial of gefitinib or gemcitabine or docetaxel chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2 or 3 (IFCT-0301 study). Lung Cancer. 2010;70(3):301-7.
11. Riely GJ, Rizvi NA, Kris MG, Milton DT, Solit DB, Rosen N, et al. Randomized phase II study of pulse erlotinib before or after carboplatin and paclitaxel in current or former smokers with advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(2):264-70.
12. Stinchcombe TE, Peterman AH, Lee CB, Moore DT, Beaumont JL, Bradford DS, 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. 2011;6 (9):1569-77.
13. Kobayashi K, Inoue A, Maemondo M, Sugawara S, Isobe H, Oizumi S, et al. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: A phase III

study (002) by North East Japan Gefitinib Study Group. J Clin Oncol. 2009; 27 (15 SUPPL. 1):8016.
14. Lee SM, Khan I, Upadhyay S, Lewanski C, Falk S, Skailes G, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2012;13(11):1161-70.
15. Mok TS, Wu Y-L, Thongprasert S, Yu C-J, Zhang L, Ladrera GE, et al. A Randomized placebo-controlled phase III study of intercalculated erlotinib with gencitabine/platinum in first-line advanced non-small cell lung cancer (NSCLC): FASTACT-II. J Clin Oncol. 2012;30(abstr 7518).
16. Agarwal S, Hirsh V, Agulnik JS, Cohen V, Mihalcioiu CL, Whittom R. A phase II study of gefitinib (G) versus carboplatin and gemcitabine (CG) in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2. J Clin Oncol. 2010;28:(abstr e18090).
17. Nokihara H, Ohe Y, Yamada K, Kawaishi M, Kato T, Yamamoto N, et al. Randomized phase II study of sequential carboplatin/paclitaxel (CP) and gefitinib (G) in chemotherapy-naive patients with advanced non-small-cell lung cancer (NSCLC): Final results. J Clin Oncol. 2008;26(abstr 8069).
18. Reck M, Von Pawel J, Fischer JR, Kortsik C, Bohnet S, von Eiff M, et al. Erlotinib versus carboplatin/vinorelbine in elderly patients (age 70 or older) with advanced non-small cell lung cancer (NSCLC): A randomized phase II study of the German Thoracic Oncology Working Group. J Clin Oncol. 2010;29(Suppl 15):abstr 7565.
19. Thomas M, Reuss A, Fischer JR, Andreas S, Kortsik C, Grah C, et al. Innovations: Randomized phase II trial of erlotinib (E)/bevacizumab (B) compared with cisplatin (P)/gemcitabine (G) plus B in first-line treatment of advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). J Clin Oncol. 2011;29:(abstr 7504).
20. Han J, Park K, Kim S, Lee D, Kim HY, Kim H, et al. First-SINGAL: First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung. J Clin Oncol. 2012;30(10):1122-8.
21. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-57.
22. Janne PA, Wang X, Socinski MA, Crawford J, Stinchcombe TE, Gu L, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol. 2012;30(17):2063-9.
23. LeCaer H, Greillier L, Corre R, Jullian H, Crequit J, Falchero L, 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. 2012;77(1):97-103.
24. Liang J, Ahn M, Kang J, Xiu Q, Chen Y, Yang C, et al. First-line treatment (txt) with pemetrexed-cisplatin (PC), followed sequentially by gefitinib (G) or pemetrexed, in Asian, never-smoker (n/smkr) patients (pts) with advanced NSCLC: An open-label, randomized phase II trial. J Clin Oncol. 2010;28(Suppl 15):abstr 7591.
25. Yang C-H, Fukuoka M, Mok TS, Wu Y-L, Thongprasert S, Saijo N, et al. 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). J Thorac Oncol. 2010;21(Suppl 8):abstr LBA2.

26. Boutsikou E, Kontakiotis T, Zarogoulidis P, Darwiche K, Eleptheriadou E, Porpodis K, et al. Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer. Onco Targets Ther. 2013;6:125-34.
27. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations. J Clin Oncol. 2011;29(abst 7519).
28. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, 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. 2010;11(2):121-8.
29. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.
30. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, 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. 2011;12(8):735-42.
31. Hirsch FR, Kabbinavar F, Eisen T, Martins R, Schnell FM, Dziadziuszko R, et al. A randomized, phase II, biomarker-selected study comparing erlotinib to erlotinib intercalated with chemotherapy in first-line therapy for advanced non-small-cell lung cancer. J Clin Oncol. 2011;29(26):3567-73.
32. Yang JC-H, Schuler MH, Yamamoto N, O'Byrne J, Hirsch V, Mok TS, et al. LUX-Lung 3: A randomized, open label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. J Clin Oncol. 2012;30(abstr LBA7500).
33. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.
34. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-8.
35. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123-32.
36. Gaafar RM, Surmont VF, Scagliotti GV, Van Klaveren RJ, Papamichael D, Welch JJ, et al. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03). Eur J Cancer. 2011;47 (15):2331-40.
37. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005;366(9496):1527-37.
38 Lee DH, Park K, Kim JH, Lee J-S, Shin SW, Kang J-H, et al. Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res. 2010 Feb 15;16(4):1307-14.

39. Lee DH, Park K, Kim JH, Lee J-S, Shin SW, Kang J-H, et al. Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res. 2010 Feb 15;16(4):1307-14.
40. Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol. 2008 Sep 10;26(26):4244-52.
41. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012 Mar;13(3):300-8.
42. Karampeazis A, Voutsina A, Souglakos J, Kentepozidis N, Giassas S, Christofillakis C, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer. 2013;119(15):2754-64.
43. Kelly K, Azzoli CG, Zatloukal P, Albert I, Jiang PYZ, Bodkin D, et al. Randomized phase 2b study of pralatrexate versus erlotinib in patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) after failure of prior platinum-based therapy. J Thorac Oncol. 2012 Jun;7(6):1041-8.
44. Okano Y, Ando M, Asami K, Fukuda M, Nakagawa H, Ibata H, et al. Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol. 2013;20(abstr 8006).
45. Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2012;30(27):3337-44.
46. Miller VA, Hirsh V, Cadranel J, Chen Y-M, Park K, Kim S-W, 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.[Erratum appears in Lancet Oncol. 2012 May;13(5):e186]. Lancet Oncol. 2012;13(5):528-38.
47. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010;11(6):521-9.
48. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol. 2010;28(5):753-60.
49 Zhang L, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): A multicentre, double-blind randomised phase 3 trial. Lancet Oncol. 2012;13(5):466-75.
50. Bylicki O, Ferlay C, Chouaid C, Lavole A, Barlesi F, Dubos C, et al. Efficacy of pemetrexed as second-line therapy in advanced NSCLC after either treatment-free interval or maintenance therapy with gemcitabine or erlotinib in IFCT-GFPC 05-02 phase III study. Journal of Thoracic Oncology. 2013;8(7):906-14.

51. Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2013;31(31):3926-34.
52. Ahn MJ, Yang JCH, Liang J, Kang JH, Xiu Q, Chen YM, et al. Randomized phase II trial of first-line treatment with pemetrexed-cisplatin, followed sequentially by gefitinib or pemetrexed, in East Asian, never-smoker patients with advanced non-small cell lung cancer. Lung Cancer. 2012;77(2):346-52.
53. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard J-Y, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected].[Erratum appears in J Clin Oncol. 2004 Dec 1;22(23):4863]. J Clin Oncol. 2003;21(12):2237-46.
54. Shi Y, Zhang L, Liu X, Zhou C, Zhang L, Zhang S, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol. 2013;14(10):953-61.