The role of the epidermal growth factor receptor tyrosine kinase inhibitors as therapy for advanced, metastatic, and recurrent non-small-cell lung cancer: a Canadian national consensus statement

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Conclusions

The EGFR-TKIs represent an additional therapy in the treatment of advanced or metastatic NSCLC. The results of ongoing clinical trials may define the optimal role for these agents and the effectiveness of combinations of these agents with other targeted agents.

KEY WORDS

Non-small-cell lung cancer, targeted therapy, epidermal growth factor receptor, tyrosine kinase inhibitor, molecular marker

1. INTRODUCTION

Lung cancer represents a major health burden in Canada. Approximately 23,300 new lung cancer cases and 19,900 deaths from lung cancer occurred in 2007, most of which were non-small-cell lung cancer (NSCLC)\(^1\). Most of these patients either present with or develop metastatic disease at some point during their illness; potentially, they are candidates for systemic therapy approaches such as chemotherapy.

Until the late 1990s, therapeutic nihilism about the benefit of systemic chemotherapy in the treatment of advanced and metastatic NSCLC was widespread. Publication of the Non-small Cell Lung Cancer Collaborative Group meta-analysis in 1995 established the association of first-line platinum-based chemotherapy with a modest improvement in survival for patients with metastatic disease\(^2\). The introduction of newer drugs such as vinorelbine, gemcitabine, paclitaxel, and docetaxel have resulted in further small improvements, although most patients still experience disease progression within a short time, with a median time to progression (TTP) of approximately 4 months\(^3\)-\(^5\).

At the time of progression following platinum-based chemotherapy, many patients maintain a good
performance status (PS) and may be candidates for further systemic therapy. Recent trials have established that second-line chemotherapy with docetaxel 6–9 improves survival and quality of life (QOL) as compared with best supportive care (BSC) and that survival of patients treated with docetaxel or pemetrexed is similar. 10. Guidelines for the management of NSCLC, including those from Cancer Care Ontario’s Program in Evidence-Based Care (CCO-PEBC) 11 now recommend either of those agents as second-line chemotherapy options 11,12.

Despite these advancements in the treatment of NSCLC, there is still a strong need for additional and better treatment options. Recently, a greater understanding of the molecular abnormalities associated with NSCLC has led to evaluation of new therapeutic targets for NSCLC. The epidermal growth factor receptor (EGFR) is one target commonly overexpressed in NSCLC. The epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib had antitumour activity, and this finding prompted their further evaluation in advanced NSCLC. 16. These agents have been evaluated extensively in phase I and II trials over the last few years, confirming the promising activity seen in phase I trials, and the TKIs have been incorporated into treatment algorithms for patients after progression on standard chemotherapy options 11.

Because of a favourable toxicity profile of the TKIs, many clinicians felt that it might be appropriate to expand their role in the treatment of advanced and metastatic NSCLC. A need therefore exists to clarify the role of EGFR-TKIs in the treatment of NSCLC. The present paper represents a consensus view of a representative sample of Canadian lung cancer medical oncologists on the role of EGFR-TKIs in the treatment of NSCLC based on a systematic review of currently available evidence.

2. MATERIALS AND METHODS

Medical oncologists specializing in thoracic oncology from five provinces across Canada were invited to participate in a consensus meeting. Six oncologists attended the consensus meeting, and three additional oncologists, plus one pathologist, provided input into the consensus process. Three key questions were identified to be addressed by the group:

- What is the role of EGFR-TKIs as first-line therapy of advanced or metastatic NSCLC as a single agent or in combination with chemotherapy?
- What is the role of EGFR-TKIs following progression after platinum-based chemotherapy (single-agent EGFR-TKI vs. BSC, EGFR-TKI vs. chemotherapy, and EGFR-TKI in combination with another agent)?
- Do any patient subpopulations, or clinical and molecular characteristics, predict for additional benefit from EGFR-TKI therapy?

2.1 Literature Search

A search of the MEDLINE database for 2000–2007 was conducted using the terms “non-small-cell lung cancer,” “epidermal growth factor receptor tyrosine kinase inhibitor,” “erlotinib,” and “gefitinib.” The search excluded articles prior to 2000, because the EGFR-TKIs are new agents and their initial phase I trials were known to be conducted during the selected time period. Conference proceedings of the American Society of Clinical Oncology 2000–2007 and the International Association for the Study of Lung Cancer 2007 World Conference on Lung Cancer were also searched. Finally, the list of included articles was reviewed by the consensus panel for omissions.

2.2 Study Selection Criteria

Articles published as full reports or as abstracts and conference presentations were included if they focused on

- EGFR-TKI alone or in combination with chemotherapy in the first-line setting,
- EGFR-TKI as second- or third-line therapy following progression of platinum-based chemotherapy, or
- clinical and molecular characteristics that may predict additional benefit from EGFR-TKI therapy.

The literature search results were reviewed by two authors (PE, FK), and articles that met the foregoing criteria were selected for retrieval. The outcomes of interest were overall survival (OS), time to disease progression, tumour response rate, molecular and clinical predictors of benefit from EGFR-TKI therapy, and QOL or symptom improvement. Single-arm phase II trials were included only if no data from randomized trials were available. Forty-three individual trials (eight phase III, eleven randomized phase II, and twenty-four single-agent phase II trials) met the eligibility criteria for the present consensus statement. Only studies published in English were considered.

2.3 External Review

Final consensus statement draft recommendations were distributed electronically to reviewers. The review panel consisted of practitioners who had attended the consensus meeting and others who were not in attendance. The comments resulting from this review were incorporated into the final document.

3. RECOMMENDATIONS AND KEY EVIDENCE

3.1 First-Line Treatment

What is the role of EGFR-TKIs as first-line therapy of advanced or metastatic NSCLC as a single agent or in combination with chemotherapy?
3.1.1 What Is the Role of Single-Agent EGFR-TKIs in Chemonaïve Patients with NSCLC?

**Key Evidence:** Fourteen single-arm phase II trials \((n = 1026)\) and one randomized phase II trial \((n = 201)\) evaluated single-agent erlotinib 150 mg or gefitinib 250 mg daily as first-line therapy of stage III/IV NSCLC (Table I). In general, patients had an Eastern Cooperative Oncology Group PS of 0–2 and were not selected for clinical or molecular characteristics reported to be associated with improved response to an EGFR-TKI. Substantial variability was observed in the response rate to single-agent EGFR-TKIs (range: 4%–55%, with an additional 20%–46% achieving disease stabilization). The time to disease progression ranged from 1 month to 6.6 months, with median survival varying between 2.9 months and 14.1 months, and 1-year survival being 24%–58.2% \(17-22,24.26.27.30-36.38,39\).

A single randomized placebo-controlled trial compared gefitinib to BSC in patients with poor performance (ps 2–3) unsuitable for chemotherapy. The observed response rate was only 6%, and the trial failed to demonstrate significant improvement in either TTF or OS \(33\). Among the trials in unselected populations, QOL and symptom improvement data were inconclusive \(17-22,24.26.27.30-36.38,39\). In the single randomized trial, the proportion of patients reporting QOL and symptom improvement appeared similar for gefitinib and BSC (21.1% vs. 20.0% and 28.3% vs. 23.3% respectively) \(33\). Several other authors also reported no significant improvement in QOL over time \(24,31\). However, Spigel reported improvement or no change in QOL [using the Functional Assessment of Cancer Therapy–Lung (FACT-L)] in 82% of patients, and improvement or control in lung cancer symptom (LCS) response in 48% of patients \(19\). Pérez–Soler reported significant improvements in pain scores at 2 weeks and improvement in emotional functioning during the first 4 weeks of therapy \(17\) (Table I). In general, these QOL analyses involved small numbers of patients in the absence of control groups and should be interpreted cautiously.

The remaining five phase II trials selected patients based on the presence of activating mutations of the EGFR gene \((n = 85)\) or of clinical characteristics associated with high response rate to treatment \((n = 40)\). The trials included patients with stage III or IV NSCLC and PS 0–2, and evaluated either erlotinib 150 mg or gefitinib 250 mg daily. Higher response rates were observed in these selected populations (range: 30%–90%) as compared with the unselected populations described earlier \(23,25,28,29,37,40\). Longer time to disease progression was also observed (5.6–13.3 months). Median survival was 15.4 months in one trial \(40\) and was either not reported or not reached in the others \(23,25,28,29,37\). This activity appears encouraging, but randomized trials comparing EGFR-TKI therapy to chemotherapy are needed to draw firm conclusions.

**Consensus Recommendation:** The evidence is currently insufficient to recommend first-line single-agent EGFR-TKI therapy in the treatment of advanced or metastatic NSCLC. These recommendations apply both to unselected populations and to patients selected on the basis of activating mutations of the EGFR gene or of clinical characteristics predictive of higher response to therapy.

There is evidence of tumour response to single-agent EGFR-TKI as first-line therapy for advanced NSCLC. Response rates to EGFR-TKI therapy appear to be higher in patients selected on the basis of activating mutations of the EGFR gene.

Randomized trials are needed to evaluate the effect of first-line EGFR-TKI on survival.

3.1.2 What Is the Role of Single-Agent EGFR-TKIs in Patients with Adenocarcinoma with Bronchioloalveolar Features?

**Key Evidence:** The literature search identified a consensus document on systemic therapy of bronchioloalveolar carcinoma (BAC) \(41\). It states that there is no evidence to confirm or refute the assertion that the sensitivity of BAC to chemotherapy is any different from that of other histologic subtypes of NSCLC.

Three phase II trials in PS 0–2 patients with stage III/IV BAC \((n = 326)\) evaluated either erlotinib 150 mg or gefitinib 250 mg daily (Table II). Patients were predominantly chemotherapy-naïve. Response rates ranged from 9% to 21%, with disease stabilization in an additional 16%–36%. The survival data demonstrated time to disease progression of between 3.0 months and 3.7 months, and median survival of 13.0–17.1 months \(42-45\). In one study, shorter progression-free survival (PFS) and OS were independently associated with non-mucinous as compared with mucinous BAC (PFS: 2.6 months vs. 11.3 months, \(p = 0.002\); OS: 10.7 months vs. not reached, \(p = 0.003\)) \(44,45\).

**Consensus Recommendation:** There is no evidence to suggest that BAC should be treated differently from other types of NSCLC. The evidence is currently insufficient to recommend EGFR-TKIs as first-line therapy for the treatment of BAC.

3.1.3 What Is the Role of First-Line EGFR-TKIs in Combination with Platinum-based Chemotherapy in Patients with NSCLC?

**Key Evidence:** Four large randomized trials evaluated EGFR-TKIs in combination with platinum-based chemotherapy in patients with good PS with stage III/IV NSCLC \((n = 4348)\), Table III. Patients were treated with either gemcitabine and cisplatin [gemcitabine 1250 mg/m² intravenously (IV) on days 1 and 8, and cisplatin 80 mg/m² IV on day 1 of a 21-day cycle] or carboplatin and paclitaxel [carboplatin area under the curve (AUC) 6 IV on day 1, and paclitaxel 200 mg/m² IV on day 1 of a 21-day cycle] with or without erlotinib 150 mg or gefitinib 250 mg or 500 mg daily. Response rates var-
| Reference                  | Design          | Treatment (daily dose) | Population      | Patients (n) | Stage $\%$ | Patients $\%$ | Response rate $\%$ | TTP (weeks) | Survival (months) | 1-Year Survival (months) |
|----------------------------|-----------------|------------------------|-----------------|--------------|------------|---------------|---------------------|-------------|-------------------|-------------------------|
| Pérez-Soler et al., 2004   | Phase II        | Erlotinib 150 mg       | Unselected      | 57           | 15.8/84.2  | 87.7/12.3    | 12/35/49            | 9           | 8.4               | 40                      |
| Kasahara et al., 2005      | Phase II        | Gefitinib 250 mg       | Unselected Asian | 30           | NR         | 0/83         | 4/36/26             | 3.3         | 10                | 43.3                    |
| Spigel et al., 2006        | Phase II        | Gefitinib 250 mg       | Unselected      | 72           | NR         | 17/27        | 9.8/36.6/53.4       | 3.7         | 6.3               | 24                      |
| Swinson et al., 2005       | Phase II        | Gefitinib 250 mg       | Unselected      | 45           | NR         | 100/0        | 15/28/58            | 32          | 82                | NR                      |
| Akerley, 2006              | Phase II        | Erlotinib 150 mg       | Unselected      | 40           | NR         |              |                     | 22          | 49 weeks          | 49                      |
| Asahina et al., 2006       | Phase II        | Gefitinib 250 mg       | Selected (EGFR+) | 16           | NR         | NR           | 75/6/19             | 8.9         | Not reached       | Not reached             |
| Giaccone et al., 2006      | Phase II        | Gefitinib 250 mg       | Unselected      | 53           | 21/79      | 85/15        | 23/30/23            | 3.0         | 13.9              | 54                      |
| Inoue et al., 2006         | Phase II        | Gefitinib 250 mg       | Selected (EGFR+) | 16           | 0/63       | 88/12        | 75/12.5/12.5       | 9.7         | NR                | NR                      |
| Lin et al., 2006           | Phase II        | Gefitinib 250 mg       | Unselected Asian | 53           | 13/87      | 76/9         | 32/21/47           | 3.2         | 9.4               | 41.5                    |
| Niho et al., 2006          | Phase II        | Gefitinib 250 mg       | Unselected Asian | 42           | 8/85       | 100/0        | 30/40/30            | NR          | 13.9              | 55                      |
| Paz-Ares et al., 2006      | Phase II        | Erlotinib 150 mg       | Selected (EGFR+) | 37           | 10/90      | 33/55        | 90/5/5              | 13.3        | NR                | 82                      |
| Reck et al., 2006          | Phase II        | Gefitinib 250 mg       | Unselected      | 58           | NR         | 76/24        | 5/40/52             | 7           | 29 weeks          | NR                      |
| Suzuki et al., 2006        | Phase II        | Gefitinib 250 mg       | Unselected Asian | 34           | 0/100      | 100/0        | 26.5/23.5           | NR          | 14.1              | 58.2                    |
| Yang et al., 2006          | Phase II        | Gefitinib 250 mg       | Unselected Asian | 44           | NR         | 40/4         | 54.5/20             | 6.3         | NR                | N                       |
| Goss et al., 2007          | Randomized phase II | Gefitinib 250 mg | Unselected | 100           | NR         | 0/100        | 6.0–/–/not available | HR: 0.82 | 95% CI: 0.62 to 1.15 |
| Hesketh et al., 2007       | Phase II        | Erlotinib 150 mg       | Unselected      | 82           | 12/88      | 0/100        | 79/36/42            | 2           | 6                 | 24                      |
| Jackman et al., 2007       | Phase II        | Erlotinib 150 mg       | ≥70 years of age | 80           | 15/85      | 90/10        | 10/41/35            | 3.5         | 10.9              | 46                      |
| Jackman et al., 2007       | Phase II        | Erlotinib 150 mg       | Selected based on patient characteristics (women) | 40           | NR         | 100/0        | 30/28/25            | 5.6         | Not reached       | NR                      |
| Jimenez et al., 2007       | Phase II        | Gefitinib 250 mg       | Unselected      | 437          | 24/76      | 70/30        | 31                  | 6.6         | 7.1               | NR                      |
| Sugio et al., 2007         | Phase II        | Gefitinib 250 mg       | Selected (EGFR+) | 16           | NR         | NR           | 50/33/–             | 8.8         | 15.4              | NR                      |

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**a** Predictor of overall response (multivariate analysis): time from last chemotherapy ($p = 0.033$); predictors of survival (multivariate analysis): time from initial diagnosis ($p = 0.0007$); good performance status (PS 0–1 / 2 ($p = 0.04$)).

**b** Partial response.

**c** 14 Patients could not be evaluated, and 1 patient experienced early death.

**d** Selected based on presence of EGFR mutations.

**PS** = performance status; **OR** = overall response (complete response + partial response); **SD** = stable disease; **PD** = progressive disease; **TTP** = median time to progression; **PFS** = median progression-free survival; **NR** = not recorded; **HR** = hazard ratio; **CI** = confidence interval; **SWOG** = Southwest Oncology Group.
ied between the trials; however, all four trials failed to demonstrate any improvement in response rate with the addition of an EGFR-TKI to platinum-based chemotherapy.\textsuperscript{46–49} Time to worsening of symptoms did not differ significantly between the groups.\textsuperscript{46,47,49}

No differences were observed in time to disease progression or in median and 1-year survival between patients randomized to chemotherapy alone and those randomized to chemotherapy plus an EGFR-TKI.\textsuperscript{46–49} (see Table III).

**Consensus Recommendation:** Clear evidence from four randomized trials shows that concurrent administration of an EGFR-TKI with first-line platinum-based chemotherapy does not prolong survival in unselected patients with NSCLC.

### 3.1.4 What Is the Role of Single-Agent EGFR-TKIs Compared with Chemotherapy in Chemonaïve Patients with NSCLC?

**Key Evidence:** Two randomized trials compared first-line therapy with an EGFR-TKI with chemotherapy in chemonaïve patients with stage I/II NSCLC and PS 0–2 (n = 299, Table IV)\textsuperscript{30,52}. Liljenbaum randomized patients with poor PS (score of 2) to treatment with either carboplatin and paclitaxel (carboplatin AUC 6 and paclitaxel 200 mg/m\textsuperscript{2} for 4 cycles) or erlotinib 150 mg daily\textsuperscript{52}. Crinò randomized elderly patients (more than 70 years of age) to vinorelbine 30 mg/m\textsuperscript{2} IV on days 1 and 8 of a 21-day cycle or gefitinib 250 mg daily\textsuperscript{50}.

Liljenbaum observed a higher response rate among patients treated with chemotherapy than with erlotinib [overall response (OR): 12\% vs. 2\%; OR + stable disease (SD): 53\% vs. 39\%]. Additionally, patients randomized to carboplatin–paclitaxel had a longer time to progression (3.5 months vs. 1.9 months) and a greater survival (9.1 months vs. 6.6 months), although these differences were not statistically significant.\textsuperscript{52}

Crinò observed similar activity from vinorelbine and gefitinib (OR: 5.1\% vs. 3.1\%; OR + SD: 53\% vs. 43\%). The PFS favoured vinorelbine, but this difference was not statistically significant [hazard ratio (HR): 1.19; 95\% confidence interval (CI): 0.85 to 1.65]. No difference in overall survival was observed (HR: 0.98; 95\% CI: 0.66 to 1.47). The groups showed no difference in overall QOL (by FACT-L) and in LCS. Gefitinib appeared to be better tolerated than vinorelbine.\textsuperscript{50}

A third trial evaluated various doses and schedules of erlotinib with carboplatin and paclitaxel.\textsuperscript{51} No significant differences were observed among the three treatment groups (Table IV).

**Consensus Recommendation:** The evidence is currently insufficient to recommend the use of an EGFR-TKI over chemotherapy in the first-line therapy of patients with NSCLC. Available evidence raises the possibility that survival of patients with poor PS treated with first-line EGFR-TKI may be less than that of patients treated with platinum-based chemotherapy.

### 3.2 Second-Line and Subsequent Treatment for Relapsed or Recurrent Disease

What is the role of EGFR-TKIs following progression after platinum-based chemotherapy (single-agent EGFR-TKI vs. BSC, EGFR-TKI vs. chemotherapy, and EGFR-TKI in combination with another agent)?

#### 3.2.1 What Is the Role of EGFR-TKIs as Second- or Third-Line Therapy Following Progression of Platinum-based Chemotherapy?

**Key Evidence:** Two guidelines developed by CCO–PERC, addressing the role of an EGFR-TKI as subsequent therapy for NSCLC, were identified\textsuperscript{11,53}. Both documents recommend the use of erlotinib as second- or third-line therapy for NSCLC patients who are not candidates for further chemotherapy.

Four randomized phase II and III trials in PS 0–2 patients with stage II/IV NSCLC who were not considered candidates for further chemotherapy examined EGFR-TKIs as subsequent therapy following progression of platinum-based chemotherapy (n = 2849, Table IV). Two large phase III studies evaluated erlotinib 150 mg (BR.21) or gefitinib 250 mg [ISEL (Iressa Survival Evaluation in Lung Cancer)] daily compared with placebo.\textsuperscript{56,57} and two randomized phase II studies [IDEAL 1 and 2 (Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2)] compared two doses of gefitinib (250 or 500 mg daily)\textsuperscript{54,55}. In the IDEAL 1 and 2 trials, no differences were observed in any outcomes examined between gefitinib 250 mg and 500 mg daily.

Results of the BR.21 and ISEL trials demonstrated that erlotinib (2.2 months vs. 1.8 months) and gefitinib (3.0 months vs. 2.6 months) significantly prolong time to disease progression.\textsuperscript{56,57} Statistically significant improvements were also seen in OS with erlotinib as compared with placebo (6.7 months vs. 4.7 months, p < 0.001)\textsuperscript{56}, and a trend toward improved survival was observed with gefitinib (5.6 months vs. 5.1 months, p = 0.087)\textsuperscript{57}.

In the BR.21 trial, patients receiving erlotinib experienced significantly longer time to deterioration in several lung cancer-related symptoms (cough, pain, dyspnea) and in overall physical function.\textsuperscript{58} In the ISEL trial, a greater proportion of patients randomized to gefitinib experienced improvement in disease-related symptoms (27\% vs. 22\%). Similarly, patients randomized to gefitinib experienced a significantly greater improvement in LCS scores (−1.38 vs. −0.86, p = 0.019)\textsuperscript{57}.

**Consensus Recommendation:** In patients with advanced or metastatic NSCLC who are not candidates for further chemotherapy, the use of an EGFR-TKI (as
# TABLE II Trials involving patients with adenocarcinoma with features of bronchioloalveolar carcinoma (BAC)

| Reference                  | Design | Population (Stage) | Patients | Treatment (daily dose) | Response rate (%) | Response rate (OR/SD/PD or Median TTP (%) | Survival 1-Year (%) | Survival 1-Year TTP (%) |
|----------------------------|--------|--------------------|----------|------------------------|-------------------|------------------------------------------|---------------------|------------------------|
| Miller et al., 2006        | Phase II | Erlotinib 150 mg BAC | 102      | Previously untreated  | 21a               | 21a                                      | 17.1                | 3.7 Months             |
| West et al., 2006          | Phase II | Gefitinib 500 mg    | 101      | Previously untreated  | 7/93              | 7/93                                     | 13                  | 4 Months               |
| Cadranel et al., 2007      | Phase II | Gefitinib 250 mg    | 88       | Previously untreated  | 0/100             | 0/100                                    | 53.4                | 13.2 Months            |

- **Response rate.**
- **Shorter progression-free and overall survival were independently associated with non-mucinous as compared with mucinous BAC (PFS: 11.3 months vs. 2.6 months; p = 0.002, OR = 0.003).**

PS = performance status; OR = overall response (complete response + partial response); SD = stable disease; PD = progressive disease; PFS = median progression-free survival; TTP = median time to progression; NR = not recorded; IFCT = Intergroupe Francophone de Cancerologie Thoracique.

# TABLE III Randomized trials of first-line epidermal growth factor tyrosine kinase inhibitors (EGFR-TKIs) in combination with platinum-based chemotherapy in patients with non-small-cell lung cancer

| Reference                  | Study  | Treatment (daily dose) | Patients | Stage (n) | Response rate (%) | Response rate (OR/SD/PD or Median TTP) | Survival 1-Year (%) | Survival 1-Year TTP (%) |
|----------------------------|--------|------------------------|----------|-----------|-------------------|----------------------------------------|---------------------|------------------------|
| Giaccone et al., 2004      | INTACT 1 | Cis–gem + placebo     | 363      | 30/6/99   | 90/10             | 47.2                                   | 6.0 Months          | 10.9 Months            |
|                            |        | Cis–gem + gefitinib 250 | 365      | 27/72     | 90/10             | 51.2                                   | 5.8 Months          | 9.9 Months             |
|                            |        | Cis–gem + gefitinib 500 | 365      | 33/67     | 90/10             | 50.3                                   | 5.5 Months          | 9.9 Months             |
| Herbst et al., 2004        | INTACT 2 | Carbo–pac + placebo   | 345      | 21/78     | 90/10             | 28.7                                   | 5.0 Months          | 9.8 Months             |
|                            |        | Carbo–pac + gefitinib 250 | 345      | 19/81     | 90/10             | 30.4                                   | 4.6 Months          | 8.7 Months             |
|                            |        | Carbo–pac + gefitinib 500 | 347      | 18/82     | 87/13             | 30.0                                   | 3.0 Months          | 7.5 Months             |
| Gatzemeier et al., 2007    | TRIBUTE | Carbo–pac + erlotinib 150 | 533      | 19/82     | 99/8.2             | 21.5                                   | 2.1 Weeks           | 4.3 Weeks              |
|                            |        | Carbo–pac + erlotinib 500 | 579      | 18/82     | 100/10             | 31.5                                   | 21.7 Weeks          | 4.3 Weeks              |
|                            |        | Carbo–pac + gefitinib 250 | 580      | 34/67     | 90/10             | 29.9                                   | 1.0 Months          | 4.2 Months             |

PS = performance status; OR = overall response (complete response + partial response); SD = stable disease; PD = progressive disease; TTP = median time to progression; NR = not recorded; INTACT = Iressa NSCLC Trial Assessing Combination Treatment; Cis–gem = gemcitabine 1250 mg/m2 intravenously on days 1 and 8, and cisplatin 80 mg/m2 intravenously on day 1 of a 21-day cycle; Carbo–pac = carboplatin AUC (area under the curve) 6 intravenously on day 1, and paclitaxel 200 mg/m2 intravenously on day 1 of a 21-day cycle; TRIBUTE = Tarceva Responses in Combination with Paclitaxel and Carboplatin.
| Reference       | Design       | Treatment                              | Patients (n) | Stage III/IV (%) | PS 0–1/2 (%) | Response rate (95% CI) (%) | TTP or PFS | Survival Median (months) |
|-----------------|--------------|----------------------------------------|--------------|------------------|--------------|-----------------------------|------------|--------------------------|
| Crinò et al., 2007<sup>a</sup> | Phase II     | Gefitinib                              | 97           | 20/80            | 76/24        | 3.1/40                      | HR: 1.19   | 1.9 months               |
|                 |              | Vinorelbine                            | 99           | 26/74            | 83/16        | 5.1/48                      | 95% CI: 0.85 to 1.65 | p=0.310 |
| Rizy et al., 2007<sup>b</sup> | Phase II     | Erlotinib 150 mg + carboplatin/paclitaxel | 87           | NR               | NR           | 18                          | 18         | 12                       |
|                 |              | Erlotinib 1500 mg + carboplatin/paclitaxel | 35           | NR               | NR           | 24                          | 35         | 16                       |
| Lilenbaum et al., 2008<sup>c</sup> | Phase II     | Erlotinib                              | 52           | 13/87            | 0/100        | 2/37/44                     | 1.9 months | 6.6<sup>c</sup>        |
|                 |              | Carboplatin + paclitaxel               | 51           | 14/86            | 0/100        | 12/41/20                    | 3.5 months | NR                       |

<sup>a</sup> Gefitinib 250 mg daily compared with vinorelbine 30 mg/m² intravenously on days 1 and 8 in a 21-day cycle.

<sup>b</sup> Erlotinib 150 mg on days 1 and 2, and carboplatin [area under the curve (AUC) 6] and paclitaxel (200 mg/m²) on day 3; erlotinib 1500 mg on days 1 and 2, and carboplatin (AUC 6) and paclitaxel (200 mg/m²) on day 3; or carboplatin (AUC 6) and paclitaxel (200 mg/m²) on day 1 and erlotinib 1500 mg on days 2 and 3. Patients received up to six 21-day cycles of treatment.

<sup>c</sup> Erlotinib 150 mg daily compared with carboplatin–paclitaxel [area under the curve (AUC) 6 and 200 mg/m² respectively] for 4 cycles.

PS = performance status; OR = overall response (complete response + partial response); SD = stable disease; PD = progressive disease; TTP = median time to progression; PFS = median progression-free survival; NR = not recorded; INVITE = Iressa in NSCLC vs Vinorelbine Investigation in the Elderly; HR = hazard ratio; CI = confidence interval.
## TABLE V
Randomized trials of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as second- or third line therapy following progression of platinum-based chemotherapy

| Reference                              | Design | Treatment          | Pts (n) | Treatment line 2 (%) | Treatment line 3+ (%) | Prior platinum/taxane (%) | Prior chemotherapy (%) | Stage I/II (%) | PS 0–1/2 (%) | Response rate (or/SD/PD) (%) | TTP (months) | Survival OS (months) | 1-Year (%) | p value |
|----------------------------------------|--------|--------------------|---------|----------------------|-----------------------|---------------------------|------------------------|----------------|-------------|-------------------------------|--------------|-----------------------------| rnd n.     |         |
| Fukuoka et al., 2003 54a (IDEAL 1)     | Phase II | Gefitinib 250      | 104     | 66                   | 44                    | 100/NR                    | NR                     | 22/88         | 88/12       | 18.4/36/41                  | 2.7          | 7.6                         | 35         | >0.05   |
|                                        |        | Gefitinib 500      | 106     | 67                   | 33                    | 100                       | NR                     | 17/83         | 87/13       | 19.0/32/42                  | 2.8          | 8.0                         | 29         |         |
| Kris et al., 2003 55b (IDEAL 2)        | Phase II | Gefitinib 250      | 102     | 0                    | 40/58                 | 100/NR                    | NR                     | 15/85         | 81/19       | 12/--/--                    | 6.0          | 24                          | 7.0        | 0.51    |
|                                        |        | Gefitinib 500      | 114     | 0                    | 42/58                 | 100                       | NR                     | 8/92          | 79/20       | 9/--/--                     | NR           | NR                         | 7.0        | 0.40    |
| Shepherd et al., 2005 56c (ISEL 21)    | Phase III | Erlotinib 150      | 488     | 51                   | 49                    | 92/NR                     | NR                     | 28            | 66/34d       | 8.9/36/45                   | 1.8          | 21                          | 6.7        | <0.001  |
|                                        |        | Placebo            | 243     | 50                   | 50                    | 91.8/NR                   | NR                     | 28            | 68/32d       | <1/27/57                    | 2.2          | 4.7                         | 7.0        | <0.001  |
| Thatcher et al., 2005 57e (ISEL)       | Phase III | Gefitinib 250      | 1129    | 49                   | 50/1                  | 96/27                     | 38                     | 44/47         | 65/29       | 8/32/37                     | 2.6          | 5.1                         | 27         | 0.087   |
|                                        |        | Placebo            | 563     | 49                   | 50/1                  | 96/28                     | 40                     | 39/50         | 68/26       | 1/31/48                     | 2.6          | 5.1                         | 27         |         |

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a Gefitinib 250 mg daily vs. gefitinib 500 mg daily.
b Gefitinib 250 mg daily vs. gefitinib 500 mg daily.
c Erlotinib 150 mg daily vs. placebo.
d Includes patients with performance status 3 (8.6% in each arm).
e Gefitinib 250 mg daily vs. placebo.

Pts = patients; PD = progressive disease; PS = performance status; OR = overall response (complete response + partial response); SD = stable disease; TTP = median time to progression; PFS = median progression-free survival; OS = overall survival; NR = not recorded; ISEL = Iressa Survival Evaluation in Lung Cancer; IDEAL = Iressa Dose Evaluation in Advanced Lung Cancer; NS = statistically nonsignificant.
compared with placebo) can result in improved survival. The use of an EGFR-TKI in patients with NSCLC who are not candidates for further chemotherapy can result in significant improvements in disease-related symptoms, and as compared with BSC alone, can delay time to symptom progression.

3.2.2 What Is the Role of EGFR-TKIs Compared with Chemotherapy Following Progression of Platinum-based Chemotherapy?

Key Evidence: Seven randomized phase II and III trials examined an EGFR-TKI as compared with chemotherapy following progression of platinum-based chemotherapy in patients with stage III/IV NSCLC and PS 0–2 (n = 2482, Table VI).

One randomized phase II trial 59 and two randomized phase III trials 62,65,66 evaluated gefitinib 250 mg daily vs. docetaxel 60 or 75 mg/m² IV every 3 weeks (n = 2096). The response rate with gefitinib was significantly higher than that with docetaxel in a Japanese population (22.5% vs. 12.8%, p = 0.009) 65,66. However, no differences were observed in response rate between gefitinib and docetaxel in the other two trials 59,62. No significant differences were observed in TTP or OS in patients treated with gefitinib or docetaxel. In the trial by Niho et al., the proportion of patients randomized to docetaxel who received third-line EGFR-TKI therapy was greater than the proportion of patients randomized to gefitinib who received third-line chemotherapy. That trial did not meet its primary outcome of non-inferiority of gefitinib (upper limit of 95% CI ≤ 1.25) as compared with docetaxel (HR: 1.12; 95% CI: 0.90 to 1.40) 65,66. However, the larger interest trial (Iressa non-small-cell lung cancer trial evaluating response and survival against Taxotere) demonstrates that gefitinib was non-inferior to docetaxel (HR: 1.02; 95% CI: 0.905 to 1.15), in which the definition of non-inferiority accepted a CI going up to 1.154 62. The proportion of patients receiving effective third-line treatment was similar between the two treatment arms in that trial.

Another four randomized phase II studies evaluated gefitinib 250 mg or erlotinib 150 mg daily with other agents (oral vandetanib 300 mg daily 60; bortezomib 1.6 mg/m² IV on days 1 and 8 of a 21-day cycle 64; vinorelbin 15 mg/m² IV on day 1, and gefitinib 250 mg daily on days 2–14 every 2 weeks 61; bevacizumab 15 mg IV on day 1 every 3 weeks; docetaxel 75 mg/m² on day 1 of a 3-week cycle; pemetrexed 500 mg/m² on day 1 of a 3-week cycle) 63 either as single agents or in combination (n = 386, Table VI). No firm conclusions can be drawn from any of these trials, although compared with erlotinib alone, the combination of erlotinib plus bevacizumab demonstrated improvement in response rate (17.9% vs. 12.2%), TTP(4.4 months vs. 3.0 months), and OS (13.7 months vs. 8.6 months) 63. A phase III trial of that combination is ongoing. Fully powered phase III trials are ongoing to compare gefitinib with vandetanib and to assess whether bevacizumab adds to the efficacy of single-agent erlotinib.

Consensus Recommendation: The evidence suggests that second-line EGFR-TKI or second-line chemotherapy results in similar survival. Sequence does not appear to be important, but if survival is the outcome of interest, the goal should be to optimize the number of patients receiving three lines of effective therapy. The evidence is currently insufficient to recommend second-line therapy with a combination of an EGFR-TKI and another targeted agent. Ongoing randomized phase III trials are currently addressing these questions.

3.2.3 How Do QOL and Symptom Control Compare in Patients Treated with Chemotherapy as Compared with EGFR-TKIs?

Key Evidence: Two of the three trials that compared gefitinib and docetaxel also examined QOL and symptom improvement 59,62.

In the SIGN trial (Second-Line Indication of Gefitinib in NSCLC), a greater proportion of patients randomized to gefitinib experienced symptom improvement as assessed by LCS (36.8% vs. 26%) and QOL improvement as assessed by the FACT-L (33.8% vs. 26%) 59. In addition, in the INTEREST trial, significantly more patients randomized to the gefitinib arm showed improvements in FACT-L score (25.1% vs. 14.7%, p < 0.0001) and trial outcome index (17.3% vs. 10.3%, p = 0.0026). Symptom improvement rates were also better with gefitinib than with docetaxel, but this difference was not statistically significant 62.

Key Recommendation: Symptom control and QOL appear to be better in patients treated with an EGFR-TKI than in those treated with either BSC or second-line chemotherapy with docetaxel. In decisions about treatment following failure of platinum-based chemotherapy, QOL and patient choice are important.

3.2.4 What Is the Role of Single-Agent EGFR-TKI Therapy in Previously Treated Patients with EGFR Gene Mutations or High Gene Copy, or EGFR Protein Expression?

Key Evidence: Four single-arm phase II trials evaluated gefitinib 250 mg daily in patient populations (n = 117) selected for the presence of activating mutations of the EGFR gene assessed by polymerase chain reaction (PCR) analysis or for high EGFR gene copy assessed using fluorescence in situ hybridization (FISH). Patients had stage III/IV disease and PS 0–2, and most had received prior chemotherapy. High response rates were observed (48%–90%) 67–70. Time to disease progression ranged from 6.4 months to 12.9 months, with a median survival of 15.5 months reported in one study 69. Given that EGFR mutations are thought to represent a favourable prognostic factor, the significance of these data are unclear, and randomized trials
| Reference          | Design       | Treatment     | Pts (n) | Treatment line 1+ (%) | Prior platinum/ chemotherapy (%) | Stage w/ (%) | PFS or yrs (%) | Response rate (%) | TTP or yrs (%) | Survival 1-Year (%) |
|-------------------|--------------|---------------|---------|----------------------|---------------------------------|--------------|-----------------|-------------------|-----------------|---------------------|
| Cufer et al., 2006 | Phase II     | Gefitinib 250 | 68      | 97                   | 91/0                            | NR           | 63/37           | 13.2              | 3.0 months      | 7.5 months          |
|                  |              | Docetaxel 75  | 73      | 99                   | 96/0                            | NR           | 71/29           | 13.7              | 3.4 months      | 7.1 months          |
| (SIGN)           |              |               |         |                      |                                 |              |                 |                   |                 |                     |
|                  | Phase II     | Gefitinib 250 | 83      | 100                  | 100/—                           | NR           | 100/—           | 11 weeks          | 11 weeks        | 6.1 months          |
|                  |              | Docetaxel 75  | 85      | 100                  | 100/—                           | NR           | 71/29           | 13.7              | 8.1 weeks        | 7.4 months          |
| Natale et al., 2006 | Phase II    | ZD6474        | 27      | 100                  | 100/—                           | NR           | 59/37           | 55.6              | 7.1 months       | 13.3 months         |
|                  |              | Gefitinib 250 | 21      | 100                  | 100/—                           | NR           | 76/24           | 52.4              | 12.8 months      | 23.4 months         |
|                  |              | Gefitinib 250 |         |                      |                                 |              |                 |                   |                 |                     |
|                  |              | + vinorelbine 15 |       |                      |                                 |              |                 |                   |                 |                     |
|                  | Phase II     | Gefitinib 250 | 733     | 100                  | 100/—                           | 26           | 14/86           | 9.1               | 2.2 months       | 7.6 months          |
|                  |              | Docetaxel 75  | 733     | 100                  | 100/—                           | 25           | 13/87           | 7.6               | 2.7 months       | 8.0 months          |
| Douillard et al., 2007 | Phase III | Gefitinib 250 | 41      | 100                  | 100/—                           | NR           | 98/2            | 12.2/27           | 3.0 months       | 8.6 months          |
| (INTEREST)      |              | Docetaxel 75  | 40      | 100                  | 100/—                           | NR           | 100/0           | 12.5/40           | 4.8 months       | 12.6 months         |
|                  |              | Bevacizumab   | 39      | 100                  | 100/—                           | NR           | 100/0           | 17.9/33           | 4.4 months       | 13.7 months         |
|                  |              | Erlotinib 150 | 50      | 100                  | 100/—                           | 100/—         | 17/—            | 2.7 months        | 1.4 months       | NR                  |
|                  |              | Erlotinib 150 | (total) |                      |                                 |              |                 |                   |                 |                     |
|                  |              | + bortezomib  |         |                      |                                 |              |                 |                   |                 |                     |
|                  | Phase II     | Gefitinib 250 | 244     | 87                   | 100/—                           | 100/—         | 19/81           | 22.5/12/66        | 2.0 months       | 11.5 months         |
|                  |              | Docetaxel 60  | 245     | 82                   | 100/—                           | 100/—         | 20/79           | 12.8/21/66        | 2.0 months       | 14.0 months         |
| Niho et al., 2007 | Phase III    | Gefitinib 250 |         |                      |                                 |              |                 |                   |                 |                     |
|                  |              | Docetaxel 60  |         |                      |                                 |              |                 |                   |                 |                     |

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**Notes:**

- Gefitinib 250 mg daily vs. docetaxel 75 mg/m² intravenously every 3 weeks.
- ZD6474 300 mg daily vs. gefitinib 250 mg daily.
- Gefitinib 250 mg daily vs. vinorelbine 15 mg/m² intravenously on day 1, and gefitinib 250 mg daily on days 2–14 every 2 weeks.
- Overall survival.
- Gefitinib 250 mg daily vs. docetaxel 75 mg/m² intravenously every 3 weeks.
- Chemotherapy (docetaxel or pemetrexed); bevacizumab 15 mg daily intravenously on day 1 of each 3-week cycle (± 5 days); erlotinib 150 mg daily for up to 52 weeks; docetaxel over 60 minutes (± 10 minutes) 75 mg/m² on day 1 of a 3-week cycle (± 5 days); pemetrexed over 10 minutes (± 5 minutes) 500 mg/m² on day 1 of a 3-week cycle.
- Erlotinib 50 mg daily vs. erlotinib 150 mg daily + bortezomib 1.6 mg/m² intravenously on days 1 and 8 of a 21-day cycle. The study was halted as required at the planned interim analysis because of insufficient clinical activity in the erlotinib + bortezomib arm.
- Gefitinib 250 mg daily vs. docetaxel 60 mg/m² intravenously every 3 weeks.

**Abbreviations:**

- Pts = Patients; PD = progressive disease; PS = performance status; OR = overall response (complete response + partial response); SD = stable disease; TTP = median time to progression; PFS = median progression-free survival; SIGN = Second-Line Indication of Gefitinib in NSCLC; NR = not recorded; INTEREST = Iressa non-small-cell lung cancer trial evaluating response and survival against Taxotere.
are needed to determine if the survival of patients with EGFR mutations or high EGFR gene copy treated with an EGFR-TKI is superior to that of similar patients treated with second-line chemotherapy.

**Consensus Recommendations:** There is evidence that patients with previously treated NSCLC and EGFR mutations or increased EGFR gene copy respond to an EGFR-TKI. However, the evidence is insufficient at this time to select patients for EGFR-TKI therapy rather than for second-line chemotherapy based on any EGFR marker.

### 3.3 Clinical and Molecular Predictors of Benefit

Do any patient subpopulations, or clinical and molecular characteristics, predict for additional benefit from EGFR-TKI therapy?

**3.3.1 What Are the Molecular Characteristics that Predict Additional Benefit from EGFR-TKI Therapy?**

**Key Evidence:** Clinical Predictors of Response to an EGFR-TKI: Table VII summarizes the trials examining clinical predictors of response. Data are available from the IDEAL 1, IDEAL 2, BR.21, and ISEL trials. Analyses from the IDEAL 1 and 2 trials demonstrated that adenocarcinoma (13% vs. 4%) and female sex (19% vs. 3%) both significantly predict response to gefitinib. Additional clinical predictors of response were observed in the BR.21 trial. In that study, clinical characteristics associated with higher response to erlotinib included adenocarcinoma (13.9% vs. 4.1%, p < 0.001), never smokers (24.7% vs. 3.9%, p < 0.001), female sex (14.4% vs. 6%, p = 0.006), and Asian ethnicity (n = 427: 18.9% vs. 7.5%, p = 0.002). Consistent with the BR.21 results, subset analysis from the ISEL trial also demonstrated that adenocarcinoma (11.9% vs. 4.8%), never smokers (18.1% vs. 5.3%), female sex (14.7% vs. 5.1%), and Asian ethnicity (12.4% vs. 7.5%) were predictors of response to gefitinib (n = 1439).

**Clinical Predictors of Survival with an EGFR-TKI:** Table VIII summarizes clinical predictors of survival for patients receiving therapy with an EGFR-TKI. In the BR.21 trial, the only characteristic which predicted greater effect on survival for erlotinib was a history of never having smoked (HR: 0.4 vs. 0.9; p = 0.02). There was no evidence of any differential survival effect for gefitinib. In a subset analysis of never smokers (n = 113) from the TRIBUTE trial evaluating the addition of gefitinib to standard first-line chemotherapy in patients whose tumour had an EGFR mutation, the presence of an EGFR mutation was associated with a nonsignificant increase in response rate. In BR.21, when only exon 19 deletion and L858R mutations were considered, the difference in response rate as compared with wild-type EGFR or other mutations was significant (27% vs. 7%, p = 0.035). The subset analysis of tumour samples from the INTACT 1 and 2 trials evaluating the addition of gefitinib to standard first-line chemotherapies demonstrated that patients whose tumours had an EGFR mutation had a higher response to chemotherapy plus gefitinib than did those without a mutation (n = 170: 72% vs. 55%, p = 0.2). Similar findings were observed in the TRIBUTE trial for patients with EGFR mutations (n = 228: 53% vs. 21%, p < 0.01), but no statistically significant
correlation was observed between response rates and mutation status in the TALENT trial. Increased EGFR gene copy or EGFR amplification also appears to be associated with an increased response rate to single-agent EGFR-TKI. The IDEAL 1 and 2 trials demonstrated that EGFR amplification was associated with a higher response to gefitinib than was seen with tumours without EGFR amplification; however, this difference was not statistically significant (n = 90; risk ratio: 29% vs. 15%; p = 0.319). Patients with an EGFR mutation or gene amplification had a significantly improved response rate as compared with patients with neither EGFR amplification nor mutation (60% vs. 10%, p = 0.0011). Within the BR.21 trial, high EGFR gene copy or amplification was also associated with a significantly higher response to erlotinib (n = 91: 21% vs. 5%, p = 0.02). Similar findings were observed in the ISEL trial (n = 317: 16.4% vs. 3.2%).

In INTACT 1 and 2, there were no differences in response with and without EGFR amplification (n = 235: 56% vs. 53%, p > 0.05). Interestingly, analysis of tumour samples from the TRIBUTE study demonstrated a lower response rate among patients whose tumours demonstrated EGFR amplification (n = 303: 8.2% vs. 3.2%). Higher response rates to erlotinib were demonstrated for patients with EGFR expression. However, the presence of KRAS mutations appears to be associated with a lower chance of tumour response. Lower response rates were observed in the BR.21 (n = 118: 5% vs. 10%, p = 0.069) and ISEL (n = 93: 0% vs. 8%) trials, although none of those results was statistically significant.

**Molecular Predictors of Survival:** Table X summarizes trials examining molecular predictors of survival for patients treated with an EGFR-TKI. No single molecular marker has consistently been associated with improved survival for patients treated with an EGFR-TKI.

The IDEAL 1 and 2 trials, BR.21, and ISEL all examined single-agent EGFR-TKIs. Analysis of tumour samples from IDEAL 1 and 2 showed no significant improvement in TTP or survival for patients with EGFR mutations or with EGFR amplification. However, these trials were not designed to examine predictors of survival, given that both groups of patients received an EGFR-TKI.

The BR.21 trial generated several reports of molecular analyses. On univariate analyses, there was no evidence that the survival benefit of erlotinib was influenced significantly by EGFR expression (n = 325: HCC+ HR: 0.68; HCC− HR: 0.93; p = 0.1), increased EGFR gene copy (n = 159: FISH+ HR: 0.43; FISH− HR: 0.80; interaction p = 0.12), or EGFR mutation status (n = 204: mut+ HR: 0.55; mut− HR: 0.74; interaction p = 0.47). However, in multivariate analysis, increased EGFR gene copy was prognostic for poorer survival (p = 0.0025) and predictive of a differential survival benefit from erlotinib (p = 0.005). The molecular analysis of the ISEL trial demonstrated a differential effect of gefitinib on survival according to EGFR gene copy (n = 370: FISH+ HR 0.61 vs. FISH− HR 1.16; interaction p = 0.045) and EGFR expression (n = 379: HCC+ HR: 0.77; HCC− HR: 1.57; interaction p = 0.049). The data were insufficient for a survival analysis for patients with and without EGFR mutations.

Molecular analyses are available from all four trials evaluating the addition of an EGFR-TKI to platinum-based chemotherapy. The addition of gefitinib to...
| Reference                  | Design | Patients (n) | Treatment                                      | Adenocarcinoma (HR) | Never smokers (HR) | Female sex (HR) | Asian ethnicity (HR) |
|----------------------------|--------|--------------|------------------------------------------------|----------------------|--------------------|-----------------|---------------------|
| Gatzemeier *et al.*, 2005  | Phase III | 1159        | Erlotinib 150 mg daily vs. chemotherapy plus erlotinib 150 mg daily | Never-smoker HR: 0.39 <i>p=0.25</i> |                   |                 |                     |
| Thatcher *et al.*, 2005    |        | 1439        | Gefitinib 250 mg daily vs. placebo              | 0.84                 | 0.69 vs. 0.92      |                 | 0.66 vs. 0.92       |
| Chang *et al.*, 2006       |        | 342         | Gefitinib 250 mg daily vs. placebo              | 0.66 vs. 0.86        | 0.37 vs. 0.85      | 0.46 vs. 0.80    | All-Asian population |
| Shepherd *et al.*, 2007    |        | 731         | Erlotinib 150 mg daily vs. placebo              | 0.7 vs. 0.8          | 0.4 vs. 0.9        | 0.8 vs. 0.8      | 0.6 vs. 0.8         |
| Douillard *et al.*, 2007   | Phase III | 1466        | Gefitinib 250 mg daily vs. docetaxel            | p>0.05               | p>0.05             | p>0.05          | p>0.05              |

HR = hazard ratio; ISEL = Iressa Survival Evaluation in Lung Cancer; TALENT = Tarceva Lung Cancer Investigation Trial; INTEREST = Iressa non-small-cell lung cancer trial evaluating response and survival against Taxotere.
| Reference               | Design   | Patients (n) | Treatment                          | EGFR Protein expression (IHC) | EGFR High gene copy (amplification ± high polysomy) | KRAS Mutations |
|------------------------|----------|--------------|------------------------------------|-------------------------------|---------------------------------------------------|----------------|
| Bell et al., 2005      | Phase II/III | 425          | Gefitinib monotherapy (250 mg vs. 500 mg daily) | n=90 | qPCR* 29% vs. 15% | n=79 |
| (IDEAL 1/IDEAL 2,      |           |              |                                    | p=0.319 | 46% vs.10% | p=0.005 |
| INTACT 1/INTACT 2)     |           |              |                                    | n=235 |                             |    |
|                        |           |              |                                    | n=170 |                             |    |
| Chemotherapy + gefitinib (250 mg daily or 500 mg daily) | qPCR* 56% vs. 53% | mut* 72% vs. 55% | p=NS |
| Bell et al., 2005      | Phase II  | 1079         | Erlotinib 150 mg daily             | n=245a |                             | n=264 |
| (IDEAL 1/IDEAL 2,      |           |              |                                    | n=228 |                             |    |
| INTACT 1/INTACT 2)     |           |              |                                    | p=NS |                             |    |
| Gatzemeier et al., 2005 | Phase III | 500          | Chemotherapy + erlotinib 150 mg daily | No difference | n=293 | n=293 |
| (TALENT)               |           |              |                                    | p=NS |                             |    |
| Hirsch et al., 2006    | Phase III | 1692         | Gefitinib 250 mg daily + carboplatin/paclitaxel | n=303 | iHC* 8.2% vs. 1.5% | n=215 |
| (ISEL)                 |           |              |                                    | iHC* 16.4% vs. 3.2% | mut* 37.5% vs. 2.6% | n=93 |
| Hirsch et al., 2007    | Phase III | 1692         | Gefitinib 250 mg daily + carboplatin/paclitaxel | n=317 | iHC* 8.2% vs. 1.5% | n=215 |
| (TRIBUTE)              |           |              |                                    | iHC* 16.4% vs. 3.2% | mut* 37.5% vs. 2.6% | n=93 |
| Zhu et al., 2008       | Phase III | 731          | Erlotinib 150 mg daily             | n=325 | 11% vs. 4% | n=204 |
| (BR.21)                |           |              |                                    | p=0.1b |                          |   |
|                        |           |              |                                    | n=159 | 21% vs. 5% | n=204 |
|                        |           |              |                                    | p=0.02b |                          |   |
|                        |           |              |                                    | mut* 27% vs. 7% | ras* 0% vs. 8% | n=206 |
|                        |           |              |                                    | p=0.16 |                          |   |

a Decrease in response.
b Univariate analysis.

IHC = immunohistochemistry; IDEAL = Iressa Dose Evaluation in Advanced Lung Cancer; INTACT = Iressa NSCLC Trial Assessing Combination Treatment; qPCR = amplification determined by an increase in gene copy by a factor of 4 or more, as assessed by quantitative polymerase chain reaction; mut* = mutation present; NS = statistically nonsignificant; FISH = fluorescence in situ hybridization showing amplification or high polysomy; TRIBUTE = Tarceva Responses in Conjunction with Paclitaxel and Carboplatin; TALENT = Tarceva Lung Cancer Investigation Trial; ISEL = Iressa Survival Evaluation in Lung Cancer.
| Reference             | Design                  | Patients (n) | Treatment                                                                 | EGFR Protein expression (IHC) | High gene copy (amplification ± high polysomy) | Mutations | KRAS Mutations |
|-----------------------|-------------------------|--------------|----------------------------------------------------------------------------|-------------------------------|------------------------------------------------|-----------|----------------|
| Bell 2005 80,a (IDEAL and INTACT) | IDEAL 1/IDEAL 2, phase II/II | 425          | Gefitinib monotherapy (250 mg and 500 mg daily) | n=90                          | No difference in survival                        | n=119b    |                |
|                       | INTACT 1/INTACT 2, phase II/II | 2130         | Chemotherapy vs. Chemotherapy + gefitinib (250 mg or 500 mg daily) | n=453                         | FISH+ HR: 2.03 95% CI: 0.67 to 6.13              | n=312     |                |
|                       |                         |              |                                                                         |                               | FISH HR: 1.01 95% CI: 0.79 to 1.29               |           |                |
|                       |                         |              |                                                                         |                               | p=NS                                             |           |                |
| Eberhard et al., 2005 82c | Phase III              | 1079         | Erlotinib 150 mg daily + carboplatin/paclitaxel vs. placebo + carboplatin/paclitaxel | n=245                         | FISH+ HR: 2.03 95% CI: 0.67 to 6.13              | n=274     | ras+ HR: 2.1   |
| Hirsch et al., 2007 84<d | TRIBUTE                |              |                                                                         |                               | FISH HR: 1.01 95% CI: 0.79 to 1.23               |           |                 |
|                       |                         |              |                                                                         |                               | p=NS                                             |           |                 |
| Gatzemeier et al., 2005 74,78 (TALENT) | Phase III           | 500          | Erlotinib 150 mg daily vs. chemotherapy + erlotinib 150 mg daily          | n=375                         | No difference in survival                        |           |                |
|                       |                         |              |                                                                         |                               | FISH HR: 0.59 95% CI: 0.35 to 0.99               |           |                |
|                       |                         |              |                                                                         |                               | p=NS                                             |           |                |
|                       |                         |              |                                                                         |                               | No difference in survival os similar in both treatment arms |           |                |
|                       |                         |              |                                                                         |                               |                                                     |           |                |
|                       |                         |              |                                                                         |                               |                                                     |           |                |
| Hirsch et al., 2006 81 (BEL) | Phase III            | 1692         | Gefitinib 250 mg daily and placebo                                       | n=379                         | FISH HR: 0.77 95% CI: 0.56 to 1.08               | n=204     | ras+ HR: 1.67  |
|                       |                         |              |                                                                         |                               | FISH HR: 0.61 95% CI: 0.36 to 1.04               |           |                 |
|                       |                         |              |                                                                         |                               | p=0.18                                           |           |                 |
|                       |                         |              |                                                                         |                               | Interaction p=0.049                                |           |                 |
|                       |                         |              |                                                                         |                               |                                                     |           |                |
|                       |                         |              |                                                                         |                               |                                                     |           |                |
|                       |                         |              |                                                                         |                               |                                                     |           |                |

Continued
| Reference          | Design         | Patients (n) | Treatment                      | Protein expression (IHC) | EGFR High gene copy (amplification ± high polysomy) | Mutations | KRAS Mutations |
|-------------------|----------------|--------------|--------------------------------|--------------------------|-----------------------------------------------------|-----------|----------------|
| Douillard et al., 2007\(^\text{a}\) | Phase III      | 1466         | Gefitinib 250 mg daily vs. docetaxel | p=NS                     | p=NS                                                | p=NS      | p=NS           |
| Garassino et al., 2007\(^\text{b}\) | (Pooled subset from INTACT, TRIBUTE, and BR.21) | 1350         | Gefitinib 250 mg daily vs. placebo | n=325 EGFR HR: 0.72     | n=578 FISH HR: 0.63                                  | mut\(^+\) HR: 0.92 | n=447          |
|                   |                |              | Erlotinib 150 mg daily vs. placebo | Interaction p=0.048      | Interaction p=0.022                                  | Interaction p=0.796 |

\(^\text{a}\) INTACT 1: Chemotherapy (gemcitabine + cisplatin, n=363) + placebo vs. chemotherapy + gefitinib 250 mg daily (n=365) vs. chemotherapy + gefitinib 500 mg daily (n=365). Gemcitabine 1250 mg/m² intravenously on days 1 and 8; cisplatin 80 mg/m² intravenously after gemcitabine on day 1 of a 21-day cycle; INTACT 2: Chemotherapy (paclitaxel + carboplatin) + placebo (n=345) vs. chemotherapy + gefitinib 250 mg daily vs. chemotherapy (n=345) + gefitinib 500 mg daily (n=347). Paclitaxel 225 mg/m² intravenously on day 1; carboplatin [area under the curve (AUC) 6] on day 1 of a 21-day cycle; IDEAL 1: gefitinib 250 mg daily (n=104) vs. gefitinib 500 mg daily (n=106); IDEAL 2, gefitinib 250 mg daily (n=102) vs. gefitinib 500 mg daily (n=114).

\(^\text{b}\) Median time to progression: EGFR mut\(^+\) > EGFR mut\(^-\). No effect on overall survival.

\(^\text{c}\) Univariate analysis.

\(^\text{d}\) TRIBUTE: Chemotherapy (carboplatin + paclitaxel) + placebo vs. erlotinib 150 mg daily. Carboplatin [area under the curve (AUC) 6] intravenously on day 1; paclitaxel 200 mg/m² intravenously on day 1 of a 21-day cycle.

\(^\text{e}\) TRIBUTE: Chemotherapy (carboplatin + paclitaxel) + placebo vs. erlotinib 150 mg daily. Carboplatin [area under the curve (AUC) 6] intravenously on day 1; paclitaxel 200 mg/m² intravenously on day 1 of a 21-day cycle.

\(\text{IHC}\) = immunohistochemistry; \(\text{IDEAL}\) = Iressa Dose Evaluation in Advanced Lung Cancer; \(\text{INTACT}\) = Iressa NSCLC Trial Assessing Combination Treatment; \(\text{TTP}\) = time to progression; \(\text{FISH}\) = fluorescence in situ hybridization showing amplification or high polysomy; \(\text{HR}\) = hazard ratio; \(\text{mut}\) = mutation present; \(\text{CI}\) = confidence interval; \(\text{NS}\) = statistically nonsignificant; \(\text{TRIBUTE}\) = Tarceva Responses in conjunction with Paclitaxel and Carboplatin; \(\text{INTEREST}\) = Iressa non-small-cell lung cancer trial evaluating response and survival against Taxotere; \(\text{ISEL}\) = Iressa Survival Evaluation in Lung Cancer; \(\text{TALENT}\) = Tarceva Lung Cancer Investigation Trial; \(\text{OS}\) = overall survival; \(\text{PFS}\) = median progression-free survival.
chemotherapy did not significantly improve OS in patients with (HR: 2.03; 95% CI: 0.67 to 6.13) or without (HR: 1.01; 95% CI: 0.79 to 1.29) EGFR amplification (n = 453), or with (HR: 1.77; 95% CI: 0.5 to 6.2) and without (HR: 0.91; 95% CI: 0.67 to 1.23) EGFR mutations (n = 312) 86.

Survival analysis from the TRIBUTE trial demonstrated a borderline improvement in TTP for patients receiving chemotherapy plus erlotinib (TTP HR: 0.59; 95% CI: 0.35 to 0.99), but no difference in OS for patients with EGFR amplification (n = 245) 82,84. In patients with an EGFR mutation, there was also a trend toward improved TTP (12.5 months vs. 6.6 months, p = 0.092), but no difference in OS was demonstrated (p = 0.96, n = 274) 82,83. Similar findings were observed in the TALEN trial. The presence of EGFR mutations did not predict for improved OS (p = 0.65 for placebo vs. p = 0.40 for erlotinib) and PFS (p = 0.74 for placebo vs. p = 0.18 for erlotinib) irrespective of treatment 74,75.

Information is more consistent that the presence of KRAS mutations is associated with worse survival for patients receiving an EGFR-TKI. Results from BR.21 demonstrated a trend towards worse survival for patients on erlotinib with KRAS mutations (n = 206; KRAS+ HR: 1.67; KRAS– HR: 0.69; p = 0.09) 71,77,85. Similarly, KRAS mutations predicted poor overall survival in erlotinib-treated patients on the TALEN trial 74,75. In addition, data from the TRIBUTE trial demonstrated that the presence of KRAS mutations was associated with significantly decreased TTP and survival in patients randomized to erlotinib plus chemotherapy (n = 274; HR: 2.1; 95% CI: 1.1 to 3.8; 4.4 months vs. 13.5 months KRAS+ vs. 12.1 months vs. 11.3 months KRAS–, p = 0.019) 82,84.

In contrast, there is no evidence that these molecular markers predict a differential effect on survival from an EGFR-TKI than from chemotherapy. The molecular analyses from the INTEREST trial showed no significant differences in survival between patients treated with gefitinib or with docetaxel according to EGFR expression, EGFR gene copy, EGFR mutational status, or KRAS status 79.

Consensus Recommendation: Molecular markers such as EGFR high gene copy or EGFR mutations and clinical characteristics such as adenocarcinoma, female sex, never smoking, and Asian ethnicity appear to be associated with a higher likelihood of response to an EGFR-TKI. The evidence is currently insufficient to select patients based on molecular markers predictive of improved survival with an EGFR-TKI. Prospective data will be needed before further recommendations can be made.

The evidence is conflicting about the predictive value of clinical characteristics for survival. However, the data suggest that the survival benefit of an EGFR-TKI may be greater among never smokers. Based on available data, molecular markers and clinical characteristics should not be used to exclude patients from receiving EGFR-TKI therapy.

4. DISCUSSION

The EGFR-TKIs represent a significant advance in the management of advanced and metastatic NSCLC. Not only do they have activity in NSCLC, they also appear to have an improved toxicity profile as compared with standard chemotherapy agents such as docetaxel. As a result, they offer an attractive therapeutic option. Nevertheless, it is important that these agents be incorporated into routine treatment algorithms based on appropriate data from randomized trials.

It is clear that EGFR-TKIs should not be used concomitantly with standard chemotherapy agents in the treatment of NSCLC. The strongest evidence supporting their use is in patients who have progressed following platinum-based chemotherapy. It is appealing to think that use of an EGFR-TKI may spare patients the toxicity of more chemotherapy. However, available data support the use of second-line chemotherapy and third-line EGFR-TKI of second-line EGFR-TKI and then third-line chemotherapy. Because both approaches prolong survival, the goal of therapy in advanced NSCLC should be to maximize the number of patients who receive three lines of therapy, if survival is the outcome of interest. However, some patients will choose not to have second-line chemotherapy, and so the sequence of therapies should reflect a discussion between the physician and the patient regarding the relative benefits and side effects of each treatment option.

Multiple reports in the literature suggest that molecular markers and clinical characteristics can be used to select patients who will be more likely to benefit from an EGFR-TKI. However, this literature comes with significant limitations. The term “benefit” creates confusion, because it is used to refer to a variety of outcomes, including tumour response, improved OS, and improved symptom control and QOL. The molecular analyses are limited to patients whose tumour samples were available. The percentage of patients whose samples were available for one or more molecular analyses ranged from 25% to 44% of the total study population. As a result, some of these comparisons involve small numbers of patients. In addition, much of the literature has focused on tumour response rates, rather than on survival. Although there is some consistency in factors predicting response, these factors do not correlate directly with variables predicting a differential benefit in survival. Considerable variation is found in the variables reported to be associated with a differential improvement in survival from therapy with an EGFR-TKI. This variation may exist in part because some of the EGFR markers are prognostic and associated with trends toward better survival (some EGFR mutations) or worse survival (high EGFR copy number). Therefore, it is not possible to assess the effect of EGFR-TKI therapy on survival in the absence of
a no-treatment control arm. Furthermore, markers that seem to predict for a differential survival benefit when EGFR-TKI therapy is compared with placebo or no treatment may not be predictive when EGFR-TKI therapy is compared with another form of treatment such as chemotherapy. As a result, the evidence is currently insufficient to recommend the routine use of molecular markers and clinical characteristics to select patients for therapy with an EGFR-TKI. It is therefore also premature to recommend the use of single-agent EGFR-TKIs as first-line therapy for NSCLC, even in patients selected on basis of molecular and clinical characteristics.

These results highlight the need for prospective trials in which tumour samples are available for all patients, so as to address correlative questions. Ongoing research will also address questions concerning the sequence of platinum-based chemotherapy or EGFR-TKI as first-line therapy.

Since the literature search for the present review was completed, preliminary data from two trials of maintenance gefitinib or erlotinib in Asian populations were presented at the American Society of Clinical Oncology Annual Scientific Meeting in 2008. Both trials showed improved OS, but no significant improvements in OS. In addition, initial results of IPASS (Iressa Pan ASia Study) were presented at the 2008 meeting of the European Society for Medical Oncology. That trial compared first-line gefitinib with carboplatin and paclitaxel in light- or never-smoking Asian patients. A significant improvement was observed in PFS, but no significant difference in OS. Other ongoing trials are evaluating the role of an EGFR-TKI as maintenance therapy in patients responding to first-line platinum-based chemotherapy.

Lastly, chemotherapy experience suggests that the therapeutic ratio can be improved with combination therapy. Preliminary evidence suggests that combination therapy with an EGFR-TKI and agents active against vascular endothelial growth factor may have greater activity. These questions are being addressed in multiple ongoing clinical trials. Participation in these trials should be encouraged.

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