Technology Assessment

Technology Assessment Program

THE RELATIVE EFFICACY OF ORAL CANCER THERAPY FOR MEDICARE BENEFICIARIES VERSUS CURRENTLY COVERED THERAPY: PART 1, GEFITINIB AND ERLOTINIB FOR NON-SMALL CELL LUNG CANCER

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Glossary

Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured.
Partial response (PR)	A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment.
Response rate (RR)	The percentage of patients whose cancers shrink or disappear after treatment. RR = CR + PR. Because CR is uncommon in NSCLC, the overall response rate is the more common measure in studies of this disease.
Stable disease (SD)	Cancer that is neither decreasing nor increasing in extent or severity.
Progressive disease (PD)	Cancer that is growing, spreading, or getting worse.
RECIST criteria	RECIST criteria are a voluntary, international standard for measuring tumor response based on measurable disease (i.e., the presence of at least one measurable lesion). RECIST criteria offer a simplified, conservative, extraction of imaging data and presume that linear measures are an adequate substitute for 2-D methods. There are four response categories: CR = disappearance of all target lesions PR = 30% decrease in the sum of the longest diameter of target lesions PD = 20% increase in the sum of the longest diameter of target lesions SD = small changes that do not meet above criteria
Overall survival	The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. Also called the survival rate.
Time to progression	A measure of time after a disease is diagnosed (or treated) until the disease starts to get worse.
Progression-free survival	One type of measurement that can be used in a clinical study or trial to help determine whether a new treatment is effective. It refers to the probability that a patient will remain alive, without the disease getting worse.
Disease-free survival	Length of time after treatment during which no cancer is found. Can be reported for an individual patient or for a study population.
Event-free survival*	Length of time after treatment that a participant in a clinical study remains free of pre-defined events. Events are defined by the study and can include adverse treatment effects, tumor recurrence/progression, or survival.
Survival rate	The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. This is commonly expressed as 5-year survival.

[†]Except as noted, these definitions were quoted from the NCI's www.cancer.gov website.

*Definition derived from http://www.intelihealth.com/IH/ihtPrint/WSIHW000/8096/8241/347567.html?d= dmtContent&hide=t&k=basePrint#efsurvival.

Introduction

Policy Context of the
Current Technology Assessment

Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) calls for a demonstration that would pay for drugs and biologicals that are prescribed as replacements for drugs currently covered under Medicare Part B. The demonstration project will be national in scope and will be limited to 50,000 beneficiaries or $500,000,000 in funding, whichever comes first. Forty percent of the funding for this demonstration will be reserved for oral anti-neoplastic drugs.

CMS has requested an assessment of the efficacy of selected oral cancer therapies included in the demonstration relative to drugs currently covered under Medicare Part B. This assessment will provide information that will be used to evaluate the likely effects of the demonstration on patient outcomes and may also provide underlying information to be used for cost-effectiveness analyses that will be completed by CMS.

The scope of the assessment will be limited to the following demonstration drugs and conditions:

- Imatinib for treatment of chronic myeloid leukemia;
- Imatinib for treatment of gastrointestinal stromal cancer;
- Gefitinib for treatment of non-small cell lung cancer;
- Thalidomide for treatment of multiple myeloma.

This report is responsive to the third item: an assessment of gefitinib for the treatment of non-small cell lung cancer. After work on this report was begun, the parameters were modified to include the closely related orally administered epidermal growth factor tyrosine kinase inhibitor, erlotinib. This was done for three reasons: 1) pivotal trial data suggested that gefitinib had little clinical efficacy; 2) a large number of studies were forthcoming on erlotinib suggesting that this drug may have greater clinical efficacy than gefitinib; and 3) erlotinib was added to the demonstration project in January 2005.

Clinical Context of the
Current Technology Assessment

An estimated 172,570 people will be diagnosed with lung cancer in the United States in 2005. [1] Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death in both men and women in this country.[1] An estimated 163,510 deaths from lung cancer will occur in 2005 in the United States, accounting for about 29 percent of all cancer-related deaths in the nation.[1] Moreover, unlike other cancers there has been no significant improvement in survival rates in the past 30 years.

There are two major types of lung cancer tumor, usually classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 84

percent of cases,[*] has clinical characteristics and treatment approaches that are distinct from SCLC, and accounts for the majority of lung cancer patients who are long-term survivors.

There is a range of treatment options (including non-curative interventions) for patients with lung cancer, and choice of treatment depends on a variety of factors including tumor type, size, and location, and the general health status of the patient. Treatments and combinations of treatments include surgery, chemotherapy, radiotherapy, and best supportive care (BSC). BSC is essentially palliative, but may include radiotherapy and occasionally chemotherapy used with non-curative intent.

Lung cancers at the time of diagnosis have already spread to regional or distant sites in more than 80 percent of cases.[1] Five-year survival is approximately 16 percent for patients with regional metastasis and approximately 2 percent for patients with distant metastases. In fact, median survival for advanced non-small cell lung cancer without treatment is only 4 months from time of diagnosis, and fewer than 20 percent of patients survive longer than the first year.

Chemotherapy, in patients with stage IV NSCLC, has been shown to improve survival and palliate symptoms. Cytotoxic agents used in treating NSCLC include platinum-based combination regimens, which are currently recommended as first-line treatment for patients with good performance status.[2,3] Furthermore, in the United States, both docetaxel and pemetrexed are approved for use as single agents in second-line chemotherapy.

The Technology

A new class of drugs has been developed that selectively inhibit the epidermal growth factor receptor tyrosine kinase (EGFR-TK). These drugs block the signal pathways involved in cell proliferation. There are two types of EGFR-TK inhibitors, the small molecules and monoclonal antibodies. Small molecules are orally active and include two drugs currently licensed in the US (Table 1): gefitinib (ZD1839, trade name Iressa™) and erlotinib (OSI-774, trade name Tarceva™). Other drugs are in development. Several monoclonal antibodies directed against EGFR-TK are under investigation, and one is currently licensed in the US: cetuximab (trade name Erbitux™). Monoclonal antibodies directed against EGFR-TK must be administered intravenously.

Gefitinib is a once daily oral medication (250-mg tablet) that was FDA-approved for use as "monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies"(Iressa™ labeling, 2004, AstraZeneca). Gefitinib received accelerated approval by the FDA conditional on the manufacturer agreeing to undertake further clinical studies in order to fully ascertain the drug's clinical benefit. Gefitinib was voluntarily withdrawn in September 2005. Erlotinib is a once daily oral medication (150-mg tablet) that is FDA-approved "for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen"(Tarceva™ labeling, 2004, OSI Pharmaceuticals). Licensure of erlotinib

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[*] Based on crude incidence rates of 52 per 100,000 for NSCLC and 60.3 per 100,000 for all lung and bronchus cancers for the years 1997-2001 (http://seer.cancer.gov/). Thus, NSCLC represents 50/60.3 x 100 = 84% of all incident lung cancer cases.

by the FDA included post-marketing obligations on the manufacturer to undertake further clinical studies.90

This report reviews all post-FDA-approval data including recently released data on the efficacy, adverse effects, and potential predictors of response related to the orally active small-molecule EGFR-TK inhibitors gefitinib and erlotinib.

EGFR-TK inhibitors have been undergoing testing for clinical uses beyond the FDA-approved indications. These include: 1) use as monotherapy for first-line treatment for advanced or metastatic NSCLC; and 2) use in combination with chemotherapy for first-line treatment for advanced or metastatic NSCLC. These agents are also under clinical investigation for use in a wide range of cancers.

Scope and Key Questions

The key questions for this review were developed with experts in the field of oncology, health economics, and health policy. The final key questions are as follows:

1. In patients with locally advanced or metastatic non-small cell lung cancer, what are the effects of gefitinib and erlotinib compared to platinum-based chemotherapy regimens on survival, disease-free survival, and quality of life?

2. In patients with locally advanced or metastatic non-small cell lung cancer who have failed to respond to platinum-based chemotherapy, what are the effects of gefitinib and erlotinib compared to docetaxel plus supportive care or best supportive care alone on survival, disease-free survival, and quality of life?

3. In patients with locally advanced or metastatic non-small cell lung cancer, what are the effects of gefitinib and erlotinib compared to platinum-based chemotherapy regimens on adverse effects, tolerability and compliance?

4. In patients with locally advanced or metastatic non-small cell lung cancer who have failed to respond to platinum-based chemotherapy, what are the effects of gefitinib and erlotinib compared to docetaxel plus supportive care or best supportive care alone on adverse effects, tolerability and compliance?

5. What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?

Methods

Search Strategy

The search strategy was constructed by combining three concepts: 1) the intervention gefitinib or erlotinib; 2) non-small cell lung cancer; and 3) prospective clinical trials. To identify the intervention concept, since these new drugs lack a specific term in the MeSH lexicon, we used text word searching for the following test strings: *gefitinib or erlotinib or Iressa or Tarceva or lapatinib or ekb-569 or ci-1033 or zd1839 or osi-774*. The lung cancer concept was implemented using the MeSH terms *lung neoplasms* (exploded) or *carcinoma, non-small-cell lung* (combined with a Boolean "or"). A published strategy, validated for finding randomized controlled trials (RCTs), was used to identify prospective clinical trials.[4] This strategy is designed to find all prospective clinical trials (maximize sensitivity), rather than to eliminate non-randomized trials (maximize specificity), and so is appropriate for this study's goal of finding phase II and III prospective clinical trials. Finally, the three concepts were combined (Boolean "or"). The strategy was executed in MEDLINE (1966 through September 2004, updated February and August 2005) and limited to articles published in the English language. The exact text of the OVID MEDLINE versions of the search strategy is provided in Appendix A.

Supplemental searches were conducted in International Pharmaceutical Abstracts and *The Cochrane Library* (CENTRAL Register of Controlled Clinical Trials and Health Technology Assessment database) and in the American Society of Clinical Oncology 2004 and 2005 annual meeting abstracts databases. Reference lists of identified studies and relevant systematic reviews and meta-analyses were hand-checked. Additional articles not indexed in the major bibliographies by August 2005 were identified through ongoing searches and discussions with field experts and monitoring new sources.

Selection Criteria

Each citation identified from the search strategies was evaluated according to the following selection criteria. Evaluations were performed by the authors.

Inclusion criteria:

Patients	Patients with locally advanced or metastatic non-small cell lung cancer who have not received chemotherapy or who have failed to respond to platinum-based chemotherapy
Interventions	Gefitinib (Iressa™ [ZD1839]) or Erlotinib (Tarceva™ [OSI-774]) or CI-1033 or Lapatinib (GW572016) or EKB-569
Comparators	Platinum-based chemotherapy regimens or docetaxel plus supportive care or best supportive care alone

Study designs:

- *For **efficacy** questions*: Prospective clinical trials; may be phase II uncontrolled, or phase III randomized controlled trials.

- *For studies of **adverse effects**:* May be retrospective or prospective case series, cohort studies, or clinical trials provided the number of patients treated (at risk for adverse effects) as well as the number with adverse effects can be ascertained.

- *For studies of **predictors** of response:* May be retrospective or prospective case series, cohort studies, case-control studies, or clinical trials provided the response can be ascertained for patients with and without the predictor.

Outcomes:

- *For **efficacy** questions*: Survival, disease-free survival, response rates and quality of life.

- *For studies of **adverse effects**:* Adverse effects, tolerability, and compliance with treatment.

- *For studies of **predictors** of response:* Predictive value of patient or tumor characteristics that are associated with clinically important differences in treatment response that are:
    1) related to the mechanism of action of the drug (i.e., molecular target); and
    2) candidates for diagnostic testing (even if not commercially or clinically available currently [e.g., Polymerase Chain Reaction])

Data Abstraction

The following data were abstracted from included studies: study design, population characteristics (including sex, age, and diagnosis), eligibility and exclusion criteria, interventions (dose and duration), outcomes assessed and results for each outcome.

We developed data collection forms in Excel (Microsoft; Redmond, WA) and summarized the data in evidence tables formatted like those in a 2003 report from the UK National Institute on Clinical Excellence (NICE).[5]

Quality Assessment

We assessed the quality of included studies by evaluating elements of internal validity (e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria).

We used as a framework the quality assessment criteria from NICE.[5] These are displayed in Appendix B. They provide specific criteria for the range of study designs used in this report including experimental studies, cohort studies, case-control studies, and case series.

Data Synthesis

In addition to a narrative description of study findings, data were reanalyzed in order to determine statistics in a common metric and display data comparatively. In particular, we recalculated measures of association between predictors and response where univariate raw data were available in order to calculate odds ratios and 95 percent confidence intervals. Such calculations were performed using Comprehensive Meta Analysis version 2.2.023 (Biostat: Englewood, NJ).

Results

The search strategy yielded 299 articles. The selection process is described below:

Identified by search strategy
(N = 299)
> |------ Excluded based on review of abstract
> | (N = 98)
> |

Included based on review of abstract
(N = 199)
> |
> |------ Excluded based on full-text review
> | (N = 86)
> | 4 case series selected on AE
> | 12 not phase II-III for efficacy
> | 3 abstract superseded by published article
> | 10 no new data reported
> | 30 no primary or original data (review article)
> | 3 wrong disease
> | 10 wrong drug
> | 12 wrong outcome
> | 1 not possible to obtain a copy of publication
> |

Included in full-text review and evidence tables
(N = 114)

The 114 included studies are comprised of 83 full reports, 30 abstract-only publications, and 1 citation in the grey literature (press releases, etc.). Study designs included 8 phase III controlled clinical trials, 14 phase II uncontrolled clinical trials, and 92 studies of other designs. The majority of the studies of other designs were retrospective series of patients receiving gefitinib under AstraZeneca's pre-approval Expanded Access Program (EAP); these provided data on adverse events and predictors, but were not included in the assessment of efficacy.

Efficacy

First-line treatment combined with standard chemotherapy
There are four completed, large, randomized controlled phase III studies that compare EGFR-TK inhibitors in combination with standard chemotherapy against standard chemotherapy alone for patients with previously untreated advanced NSCLC (Table 2).[6-9] Two of these used gefitinib[6,7] and two, which have only been presented in abstract form, used erlotinib.[8,9] The patient population and design of the studies were nearly identical except the studies with gefitinib used two different doses, 250 mg and 500 mg daily, in a three-arm study, while the erlotinib studies used a single dose. The chemotherapy used in the paired studies with each drug was standard combination chemotherapy of either carboplatin and paclitaxel in the North American study,[6,8] or cisplatin and gemcitabine in the study done outside North America.[7,9] None of the four studies

showed a statistically significant difference in overall response rate (CR + PR) (Table 3), time to treatment failure (or progression-free survival), or overall survival (Table 4) between the EGFR-TK arm(s) and the placebo arm. Unpublished subgroup analysis of one study[8] by smoking status showed an increase of median survival from 10 months in the placebo group to 22 months in the erlotinib-containing combination arm among the 8 percent of patients in the study who had never smoked. We are not aware of results of a similar analysis in the other three studies.

In addition to the phase III studies, a single, small, uncontrolled phase II study of docetaxel 75 mg/m^2 plus gefitinib 250 mg daily in patients at least 70 years of age reported a response rate of 50 percent.[10]

First-line treatment as single agent
Eleven uncontrolled studies of gefitinib or erlotinib as a single agent in previously untreated patients with advanced NSCLC were identified (Table 5), seven of which[11-17] were in unselected patients. Two of the studies were restricted to patients with bronchoalveolar carcinoma (BAC) histology,[18,19] one included only patients age 70 and greater,[20,21] and the remaining study required patients to have poor performance status (PS 2-3).[22] The trials in unselected patients included a total of 293 patients and reported response rates ranging from 5 percent to 61 percent but with most falling between 25 percent and 33 percent (Table 6). The two studies in patients with BAC histology included patients who had been previously treated, but only one of these studies[18] has yet reported the results separately for these two groups. The overall response rate in the two studies of BAC with gefitinib 500 mg daily and erlotinib 150 mg daily was 18 percent and 24 percent, respectively. In the study of gefitinib 500 mg daily, patients without prior treatment had a response rate of 21 percent compared to 10 percent in previously treated patients; however, the overall survival of the two groups was similar. In the study restricted to previously untreated elderly patients with advanced NSCLC, a response rate of 12 percent was reported.[21] Finally, in a single study (18 evaluable patients) of patients with poor performance status, no responses were observed.[22]

Survival data among all groups of studies show median survival of 10 to 12 months; some studies reported 1-year survival which ranged from 43 to 76 percent. Notably, compiled data from the EAP showed a median survival of 6 months and 1-year survival rate of 29.7 percent.[23]

Second- or third-line treatment
Two randomized, placebo-controlled trials of single agent EGFR-TK inhibitors in previously treated patients have been completed and reported in preliminary form (Table 7). Both studies provided best supportive care to patients on both arms. In the BR21 trial, patients received either erlotinib 150 mg daily or placebo.[24,25] As expected based on the earlier phase II study of erlotinib, the response rate (complete response plus partial response) was 9 percent versus < 1 percent in the placebo arm (Table 8). The median survival of 6.7 months in the erlotinib arm was 2 months longer than the placebo arm (Table 9). Progression-free survival and overall survival also significantly favored the erlotinib arm, with hazard ratios of 0.61 and 0.70, respectively. Multiple subgroup analyses indicated a survival advantage in every group examined except smoking status and possibly EGFR expression. The survival benefit among non-smokers (21 percent of subjects) was significantly greater than among the current or former smoker subgroup. Although survival was better among the smoker subgroup in the erlotinib

arm, this advantage did not reach statistical significance. The availability of appropriate tumor tissue from only one-third of study subjects limited the analysis of EGFR expression correlation with survival, which suggested the possibility of a greater survival benefit in the EGFR-positive group. In contrast, a larger study of gefitinib in previously treated patients, which has been reported only as a press release from the pharmaceutical sponsor,[26] failed to demonstrate a statistically significant advantage for the gefitinib-treated group (hazard ratio = 0.89, p = 0.11). Subgroup analysis suggested survival advantage in never smokers and East Asian patients, but not among those with adenocarcinoma. No quantitative estimates are available in the limited reporting in the press release; further analyses and more detailed reporting are expected.

Of six prospective phase II studies of EGFR-TK inhibitors in patients with advanced, previously treated NSCLC, four used gefitinib and two erlotinib (Table 7). Patients in two gefitinib studies were randomized to either 250 mg or 500 mg daily, while the third used only the 250 mg dose. Response rates were not significantly higher in the 500mg arms (Table 8). For the 250mg dose arms, objective response rates were 12 percent and 18.5 percent in the randomized dose comparisons, and 5 percent, 10 percent and 12 percent in the other phase II trials. Median survival was 7 and 8 months in the two larger studies, compared to 5 and 4 months in the others (not reported in one). The lower response rates in the latter studies suggest that patient selection may contribute to observed tumor response (Table 9). The two phase II studies of erlotinib found objective response rates of 10 percent and 12.3 percent.[27,28] One erlotinib study required patients to have tumor samples that expressed EGFR, while the other, like the phase II gefitinib studies, did not. In this study of 57 patients,[27] a response rate of 12.3 percent and median survival of 8.4 months was similar to those in the larger gefitinib studies.

Quality of life

Quality of life data were reported for some of the clinical trials of EGFR-TK inhibitors (Table 10). The only controlled trial demonstrated a significant average improvement in quality of life symptom measures associated with erlotinib versus placebo[24,25] Other data on erlotinib and all data on gefitinib are uncontrolled.[29-31]

No studies directly compared quality of life outcomes associated with EGFR-TK treatment to those associated with cytotoxic chemotherapy; however, two controlled trials suggest that improvements in quality of life measures can also occur with pemetrexed or docetaxel regimens.[32,33] However, while the majority of patients in the pemetrexed and docetaxel arms were stable or improved, the proportions worsening (33 percent and 27.9 percent) exceeded the proportions that improved (21.2percent and 21.6 percent) in each arm.[32] Based on these data, this study would likely not show average improvement in quality of life. Shepherd et al.,[33] using the EORTC QLQ-C30 instrument with the LC13 lung cancer module, a disease-specific quality of life measure, found a trend toward less deterioration in quality of life measures associated with docetaxel than with best supportive care; however, this effect was not statistically significant. The sparse data on quality of life outcomes, the wide variety of quality of life measures, and the lack of direct comparative trials makes the comparison between gefitinib and docetaxel in terms of quality of life outcomes uncertain.

Efficacy data are available for studies of other cytotoxic chemotherapies in previously treated patients with NSCLC (Table 11). Docetaxel has been shown to have survival advantage over

best supportive care[33] and over vinorelbine or ifosfamide,[34] with identical survival outcomes to pemetrexed.[32] No prospective clinical trial data (phase III or phase II) are available for any treatments beyond second-line. Massarelli et al.[35] describe similar survival associated with various third- and fourth-line chemotherapy regiments in a small retrospective study.

These trials of traditional chemotherapy have similar inclusion criteria and similar demographic characteristics to Shepherd et al.[25] (erlotinib vs. placebo), but tend to have fewer patients with PS≥2 (ranging from 11 percent to 24 percent vs. 35 percent) and fewer patients with ≥ 2 prior chemotherapy regimens (ranging from 25 percent to 35 percent vs. 49 percent). The ISEL study (gefitinib vs. placebo) is not reported in sufficient detail to evaluate the comparability of the patient populations. The differences noted might lead one to expect slightly poorer survival in the EGFR-TK trials as compared to these second- and third-line chemotherapy trials; however, such indirect comparisons are subject to biases (due to unmeasured or unreported factors) that may be greater than the effects of the variables noted.

Adverse Effects/Harms

Adverse effects associated with EGFR-TK inhibitors and comparison treatments are described in Table 12. The most common adverse effects of EGFR-TK inhibitors are skin toxicity and diarrhea. The skin toxicity is predominantly rash and to a lesser extent acne, pruritus, and other dermatologic reactions. For gefitinib, toxicity was more common at the higher 500 mg daily dose. Approximately half to two-thirds of patients experienced rash, and about half had diarrhea with gefitinib 250 mg. Erlotinib toxicity was somewhat more common than gefitinib toxicity; however, estimates of erlotinib toxicity are based on the results of the single published phase II trial.[31] For both drugs, less than 5 percent of toxicity was grade 3 or higher. Other consistently reported toxicity included hypertransaminasemia (2 percent to 12 percent) and an uncommon interstitial lung toxicity (< 1% percent). These toxicities compare favorably to those of traditional cytotoxic agents.

Predictors of Response

All reports on predictors of response or survival from EGFR-TK inhibitor clinical studies are shown in Tables 13 and 14. Predictors of response to EGFR-TK inhibitors were distinguished from prognostic factors, which are associated with survival. The latter were not of primary interest for this report, as the prognostic factors reported in the examined studies have generally been known for decades and are not specific to EGFR-TK inhibitors. Response predictors considered were predictors of a higher likelihood of objective tumor response (in phase II and phase III studies) or identifiers of a subgroup with differential treatment effect (for phase III studies). Clinical factors reported as being tested for association with either response or survival are shown in Table 13. Those characteristics that were initially identified as associated with a higher response rate in more than two studies included female sex and never smoking status. Studies examining the association between these factors and response are detailed in Table 15. For sex, there is a consistent association between female sex and a doubled likelihood of

response. For smoking, the effect is less consistent between studies but is, on average, stronger than that observed for sex.

Two factors had more than one study reporting an association with response: age over 70 years and East Asian ethnicity. The associations with age were not consistent in direction with some studies finding older patients more likely to respond and some studies reporting younger patients having the higher response rate. East Asian ethnicity was associated with higher responses in 2 of 3 studies reporting on this factor; this finding is consistent with data showing a higher incidence of EGFR mutation in East Asian NSCLC patients.

Two other factors have received some attention in the literature: rash and performance status. However, for rash, the associations are weak and not statistically significant in the few studies reporting on the association. Performance status is an extremely important general prognostic factor, but did not have any consistent association with likelihood of tumor response among the seven studies reporting this association.

Tumor characteristics potentially predictive of response or survival are shown in Table 14. Adenocarcinoma histology and its subtypes of BAC and papillary type were associated with better response in about half of studies. Contrary to initial expectations of many of the investigators, the majority of studies examining EGFR expression did not associate EGFR expression with response. Also, no reproducible association was found between response and the related receptor TK; Her2/neu (erbB2), which forms heterodimers with EGFR; the activated form of EGFR (p-EGFR); or the activated downstream signaling molecules (p-Akt, p-Erk/p-MAPK, and p-STAT3). In contrast, nineteen studies have found a strong positive association between presence of somatically acquired mutation of the active site of EGFR and response to gefitinib or erlotinib (Table 16). The biological plausibility of this association is strengthened by the finding of secondary mutations of EGFR in tumors from patients with secondary resistance to EGFR-TK inhibitors. Furthermore, the EGFR mutations occur preferentially in the demographic groups with highest response rates to EGFR-TK inhibitors, most notably non-smokers but also women and East Asians, as well as patients with adenocarcinoma histology. However, findings from the BR21 study of erlotinib (the only randomized trial to show an overall survival benefit from EFGR-TK inhibitors), showed no association of EGFR mutation and survival benefit. Additional molecular predictors of response and survival benefit are being investigated including EGFR gene copy number. While KRAS mutations were associated with non-response in preliminary reports, [36,37] few data are yet available to confirm this negative association with response.

Discussion

The use of EGFR-TK inhibitors in NSCLC is a rapidly evolving field; much of the data addressing the key questions of this report has become available since the key questions were formulated just over a year ago. In this section we summarize the findings of the review in terms of answering the key questions initially posed, and then discuss the clinical and research implications of these data.

1. *In patients with locally advanced or metastatic non-small cell lung cancer, what are the effects of gefitinib and erlotinib compared to platinum-based chemotherapy regimens on survival, disease-free survival, and quality of life?*

> There is good evidence from four RCTs that addition of either gefitinib or erlotinib to combination chemotherapy does not improve survival or disease-free survival for patients with previously untreated, advanced non-small cell lung cancer. While quality of life results have not been published from any of the four randomized studies, it is unlikely that quality of life would be improved by the addition of an agent known to induce toxicity without concomitant improvement in the quantity of life. Based on an unpublished subgroup analysis, one study suggested that non-smokers may benefit from the addition of erlotinib to chemotherapy. However, this is not currently supported by completed prospective studies.

> First-line treatment alone (i.e., not in combination with traditional cytotoxic chemotherapy) has been studied only in phase II (uncontrolled) trials; each of these studies has important limitations such as small number of patients or limited generalizability due to special populations (elderly, poor performance status, BAC histology). Few complete responses were observed in these studies, and the rates of partial responses observed are no higher than those observed in studies using traditional chemotherapy. These data, although limited in terms of quality and generalizability, do not suggest that first line treatment with EGFR-TK inhibitors in unselected patients is beneficial compared to traditional chemotherapy.

2. *In patients with locally advanced or metastatic non-small cell lung cancer who have failed to respond to platinum-based chemotherapy, what are the effects of gefitinib and erlotinib compared to docetaxel plus supportive care or best supportive care alone on survival, disease-free survival, and quality of life?*

> A single RCT of gefitinib versus placebo in patients with previously treated (second- or third-line) advanced NSCLC was reported through a press release not to show a survival benefit for gefitinib.[25,26] While the hazard ratio of 0.89 favored gefitinib, this was not statistically significant (p = 0.11). The effect of gefitinib on progression-free survival or quality of life has not been reported. A single RCT of erlotinib versus placebo in a similar clinical setting did show a survival benefit that was statistically significant with a hazard ratio of 0.73 (p = 0.0001).[24 25] Median survival was 6.7 months in the erlotinib arm compared to 4.7 months in the placebo arm. Progression-free survival also significantly improved with erlotinib. The reported quality-of-life analysis was limited to determination of the effect of erlotinib on the time to deterioration of three symptoms (cough, dyspnea, and pain). For each measure, there was improvement in the erlotinib arm compared to placebo. In both studies,

all patients received best supportive care. There are no completed studies of gefitinib or erlotinib compared to docetaxel or other cytotoxic agents for this clinical setting for directly assessing the relative effect of EGFR-TK inhibitors with cytotoxic agents, such as docetaxel. As a point of reference for comparison, an RCT of two different doses of docetaxel versus best supportive care alone favored docetaxel over the control arm, especially at the lower dose (75 mg/m^2).[33] Median survival time improved from 4.6 months in the control arm to 7.5 months with docetaxel 75 mg/m^2, while it was 5.9 months in the 100-mg/m^2 arm. The lower dose is widely adopted as the appropriate dose due to several deaths due to drug-related toxicity at the higher dose. A second RCT compared docetaxel 75 or 100 mg/m^2 with a control arm of either vinorelbine or ifosfamide, neither of which has been shown to improve outcomes in this clinical setting.[34] The median survival in the docetaxel arms were 5.8 and 6.6 for the 75 and 100 mg/m^2 doses, respectively, compared to 5.4 months in the control arm. Comparing the median survival times between the erlotinib RCT and the two docetaxel trials does not demonstrate a clear advantage for one drug; however, such comparisons are of limited utility. One of the docetaxel RCTs included quality of life data that has been published, but the measures used were distinct from that used in the erlotinib trial, which severely limits the ability to compare between trials.

Several possible explanations have been proposed for the divergent results from the two similar studies in patients with previously treated NSCLC that used what was previously thought to be two similar drugs. First, the trials differed with respect to the drug dosage relative to the maximal tolerated dose, which may have resulted in less inhibition of EGFR in the gefitinib study. The more potent erlotinib was administered at the maximal tolerated dose, whereas the gefitinib dose was selected to achieve an optimal biologic dose. Second, there may have been important differences in the patients between the two studies, in particular with respect to smoking status. The fraction of never smokers in the ISEL study (gefitinib vs. placebo) has not been reported, while that in BR21 (erlotinib vs. placebo) was 20 percent, higher than is typical among patients with NSCLC in North America. Final reports of the ISEL study will need to be scrutinized for smoking status and method of ascertainment. Other differences in study populations such as prior chemotherapy and presence of KRAS mutations may also be related to differences in the results of these two trials. Finally, the difference may simply be stochastic.

3. *In patients with locally advanced or metastatic non-small cell lung cancer, what are the effects of gefitinib and erlotinib compared to platinum-based chemotherapy regimens on adverse effects, tolerability and compliance?*

The toxicity of gefitinib and erlotinib alone has not been directly compared with platinum-based chemotherapy in previously untreated patients with advanced NSCLC. However, the addition of gefitinib to chemotherapy in this clinical setting in two RCTs resulted in additive toxicity, but did not significantly limit the ability to deliver the chemotherapy or compliance with gefitinib. Similar results were presented in preliminary format with erlotinib.

4. *In patients with locally advanced or metastatic non-small cell lung cancer who have failed to respond to platinum-based chemotherapy, what are the effects of gefitinib and erlotinib compared to docetaxel plus supportive care or best supportive care alone on adverse effects, tolerability and compliance?*

The toxicities of gefitinib and erlotinib are sufficiently distinct from those of docetaxel that it is possible to infer differences in the adverse effects of these two classes of agents based on indirect comparison between trials. The toxicity of gefitinib and erlotinib is primarily dermatologic and diarrhea, and is less than grade 3 toxicity in all but several percent of patients taking these agents. Drug-related mortality is less than 1 percent. In contrast, docetaxel is associated with grade 3 toxicity in more than 10 percent of subjects for hematologic toxicity (primarily neutropenia), neurosensory toxicity, asthenia, and pulmonary toxicity.

5. *What patient or tumor characteristics distinguish treatment responders from non-responders and have potential to be used to target therapy?*

There was the expected lack of uniformity of possible prognostic factors across studies with regard to grouping for analysis and variable inclusion of different factors within a particular study. We therefore first reviewed studies to identify the number of studies that included a particular prognostic factor and then further examined the factors that were most commonly found to be associated with response.

The strongest patient characteristics predicting response to gefitinib or erlotinib therapy appear to be smoking status and sex; each of which is supported by several studies showing statistically significant associations with response. The development of rash during treatment was also associated with response in some studies, but is, of course, not a characteristic available at baseline that could be used to select patients for treatment. The magnitude of the association for predictors of response is, for the most part, relatively small; few exceed a relative risk of 2. Publication bias favoring studies reporting positive associations may tend to exaggerate the strength of association. For smoking status, one study[38] suggested a dose-response with smoking: never (63 percent response), moderate (23 percent response), and heavy (16 percent response). A similar trend was observed with rash: grade 0 (12 percent response), grade 1 (33 percent response), and grade 2 (46 percent response). East Asian ethnicity was also associated with increased likelihood of response in a few studies that reported this variable.

Among the tumor characteristics, EGFR mutations were most strongly and consistently associated with response, with a risk ratio of response varying between studies from 1.3 to 9.7. While most of the studies were small, the total number of patients studied for EGFR mutations (a total of 312 patients with mutation and 816 without mutation in 22 studies) has grown rapidly over that last 6 months. This relatively expensive assay is now clinically available. Histologic subtype of adenocarcinoma and its various subtypes were also associated with response. Histology was classified differently among the studies examining this factor, with most comparing response in adenocarcinomas versus non-adenocarcinoma,

while several considered specific subtypes of adenocarcinoma, particularly BAC, but also papillary adenocarcinoma in one study.

Current State of Clinical Use

Gefitinib use in clinical practice is currently declining given the disappointing results of the Iressa Survival Evaluation in Lung cancer (ISEL) study, which failed to show a survival benefit for gefitinib compared with best supportive care.[26] Patients currently receiving gefitinib are being continued on therapy, but new patients are not being started except when they have characteristics that predict increased likelihood of response (e.g., never smokers, women with adenocarcinoma, EGFR mutation). Erlotinib is a treatment option for patients in second- or greater line of therapy and for selected patients (e.g., never smokers, women with adenocarcinoma) for first-line therapy. Combination of an EGFR-TK with chemotherapy or radiotherapy is not currently recommended outside a clinical trial.

Projections for Future Clinical Use

Erlotinib will continue to be used as a treatment for previously treated patients. Gefitinib's use will likely be limited to subgroups of previously treated patients or may ultimately be completely supplanted by erlotinib. AstraZeneca recently withdrew their Marketing Authorization Application (MAA) with the European Medicines Agency; while acknowledging that it may consider a new MAA after the full ISEL data set is evaluated.[39]

Implications for Future Research

The identification of EGFR mutations in the NSCLC tumors of never smokers and their association with response to EGFR-TK inhibitors suggests that the differentiation of subgroups of NSCLC may now have important implications for therapeutic decision making. An important question to be addressed is the role of erlotinib in the treatment of smokers or those without EGFR mutation. Studies are now being initiated to examine EGFR-TK inhibitors as first-line therapy in patients selected on the basis of clinical or tumor characteristics. Recent early findings extending the association of EGFR mutation with response include increased gene copy numbers associated with response [40-42] KRAS mutations associated with lack of response[36,37] and secondary EGFR mutations associated with acquired resistance [43,44] will also likely be active areas of inquiry into the use of genetic testing not only for initial treatment selection, but ongoing treatment decision making.

Ongoing studies will also address the role of EGFR-TK inhibitors in treatment of patients with earlier stage disease. The combination of EGFR-TK inhibitors with other targeted agents is being studied. New EGFR-TK inhibitors are being investigated which may have distinct roles either by targeting multiple members of the EGFR family or by having different activity for the various EGFR mutations.

Table 1. EGFR-TK inhibitors

Generic name	Trade name [development name]	FDA-approved indications	Dosage	Mechanism of action
Gefitinib	Iressa™ [ZD1839]	Advanced NSCLC	250-500 mg PO daily	Inhibits the intracellular tyrosine kinase (TK) of epidermal growth factor receptor (EGFR), resulting in cell cycle arrest, apoptosis, and inhibition of angiogenesis and tumor cell invasion
Erlotinib	Tarceva™ [OSI-774]	NSCLC	150 mg PO daily	
-	Not marketed [CI-1033]	Not yet approved		
Lapatinib	Not marketed [GW572016]	Not yet approved		
-	Not marketed [EKB-569]	Not yet approved		

Abbreviations: EGFR-TK = epidermal growth factor receptor tyrosine kinase; FDA = Food and Drug Administration; NSCLC = non-small cell lung cancer; PO = per os (by mouth)

Table 2. First-line treatment with EGFR-TK inhibitors combined with cytotoxic agents for patients with advanced NSCLC

Study ID	EGFR-TK inhibitor dose [length of follow up]	Chemo-therapy	No. of patients, age (median [range]), sex*	Histology	Stage	PS	Smoking status	Outcomes sought
Phase III								
Herbst et al., 2004[6]	Gefitinib 250-500 mg/day [12 months]	Carboplatin AUC 6 mg/ml-min & paclitaxel 225 mg/m^2 x 6 cycles	1037 pts 62 (26-86) 40% F	Squamous 19.4% Adeno 51.9% Adenosquamous 1.7% BAC 3.2% NSCLC NOS 11.3% Large cell 11.0	IIIA 3.8% IIIB 17.1% IIIB no pl eff 5.2% IIIB pl eff 11.9% IV 78.3%	0: 38.8% 1: 51.9% 2: 9.3%	NR	1. Overall survival 2. TTP Others: response rate, disease-related symptoms and QoL, toxicity
Giaccone et al., 2004[7]	Gefitinib 250-500 mg/day [16 months]	Cisplatin 80 mg/m^2 & gemcitabine 1250 mg/m^2 x 6 cycles	1093 pts 60 (31-85) 26% F	Squamous 29.2% Adeno 46.6% Adenosquamous 1.4% BAC 0.3% NSCLC NOS 11.8% Large cell 8.8%	IIIA 1.9% IIIB 28.4% IIIB no pl eff 6.6% IIIB pl eff 21.8% IV 68.6%	0: 33.9% 1: 55.6% 2: 9.6%	NR	1. Survival 2. TTP, response, toxicity
Miller et al., 2004[8]	Erlotinib 150 mg/day [22 months]	Carboplatin/ paclitaxel (6 cycles)	1059 pts 62.6 (24-84) 38% F	Squamous 16% Adeno 61% Large cell 10% NSCLC NOS 12%	IV 82%	0: 36.2% 1: 63.6% 2: 0.2%	Never: 8%	1. Overall survival; Others: TTP, response rate, duration of response
Gatzemeier et al., 2004[9]	Erlotinib 150 mg/day [NR]	Cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2 x 6 cycles	~1150 NR NR	NR	NR	0/1: 100%	NR	1. Survival Others: TTP, toxicity
Phase II								
Williams et al., 2004[10]	Gefitinib 250 mg/day [NR]	Docetaxel 75 mg/m^2 every 3 weeks	12 pts 74 (70-82) 25% F	NR	NR	NR	NR	Response, survival

*Patient characteristics based on placebo group when not reported for all patients in randomized controlled trial.

Abbreviations: Adeno = adenocarcinoma; AUC = area under the curve; BAC = bronchoalveolar carcinoma; EGFR-TK = epidermal growth factor receptor tyrosine kinase; F = female; No. = number; NR = not reported; NSCLC NOS = non-small cell lung cancer not otherwise specified; pl eff = pleural effusion; PS = performance status; pts = patients; TTP = time to progression

Table 3. Summary of tumor response in studies of first-line treatment with EGFR-TK inhibitors combined with cytotoxic agents for patients with advanced NSCLC

Study ID	Diagnosis (no. of patients)	Chemotherapy (all patients)	Sub-groups	Tumor response				
				% CR	% PR	% SD	% DP	% NE
Phase III								
Herbst et al., 2004[6]	NSCLC (345) (345) (347)	Carboplatin AUC 6 mg/ml x min and paclitaxel 225 mg/m^2 x 6 cycles	Placebo Gefitinib 250 mg/day Gefitinib 500 mg/day	1.2 2.6 0.6	28.7 30.4 30.0	- - -	- - -	- - -
Giaccone et al., 2004[7]	NSCLC (363) (365) (365)	Cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2 x 6 cycles	Placebo Gefitinib 250 mg/day Gefitinib 500 mg/day	0.9 3.3 2.1	46.3 47.9 48.2	- - -	- - -	- - -
Miller et al., 2004[8]	NSCLC (533) (526)	Carboplatin/ paclitaxel (6 cycles)	Placebo Erlotinib 150 mg/day	No differences between groups	- -	- -	- -	- -
Gatzemeier et al., 2004[9]	NSCLC (~575) (~575)	Cisplatin 80 mg/m^2 and gemcitabine 1250 mg/m^2 x 6 cycles	Placebo Erlotinib 150 mg/day	NR	NR	NR	NR	NR
Phase II								
Williams et al., 2004[10]	NSCLC (12)	Docetaxel 75 mg/m^2 every 3 weeks	Gefitinib 250 mg/day	0	50	30	20	-

Abbreviations: CR = complete response; DP = disease progression; EGFR-TK = epidermal growth factor receptor tyrosine kinase; NE = not evaluable; NSCLC = non-small cell lung cancer; no. = number; PR = partial response; SD = stable disease

Table 4. Summary of patient survival in studies of first-line treatment with EGFR-TK inhibitors combined with cytotoxic agents for advanced NSCLC

Study ID	Diagnosis (no. of patients)	Sub-groups (dosage in mg/day)	Survival from start of treatment			Progression-free survival		
			Median (months)	1-year (%)	HR (95% CI) [p-value]	Median TTP (months)	1-year (%)	HR (95% CI) [p-value]
Herbst et al., 2004[6]	NSCLC							
	(345)	Placebo	9.9	42	NS	5.0	-	NS
	(345)	Gefitinib 250	9.8	41		5.3	-	
	(347)	Gefitinib 500	8.7	37		4.6	-	
Giaccone et al., 2004[7]	NSCLC							
	(363)	Placebo	10.0	44	NS	6.0	-	NS
	(365)	Gefitinib 250	9.9	41		5.8	-	
	(365)	Gefitinib 500	9.9	43		5.5	-	
Miller et al., 2004[8]	NSCLC							
	(533)	Placebo	10.5	-	0.995	4.9	-	0.937
	(526)	Erlotinib 150	10.6	-	[p = 0.95; NS]	5.1	-	[p = 0.36, NS]
Gatzemeier et al., 2004[9]	NSCLC							
	(~575)	Placebo	10.2	-	NS	5.9	-	NS
	(~575)	Erlotinib 150	9.9	-		5.5	-	

Abbreviations: CI = confidence interval; EGFR-TK = epidermal growth factor receptor tyrosine kinase; HR = hazard ratio; no. = number; NS = not statistically significant; NSCLC = non-small cell lung cancer; TTP = time to progression

Table 5. First-line treatment with EGFR-TK Inhibitors (single agent) for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Histology	Stage	PS	Smoking status	EGFR-TK inhibitor dose/day	Outcomes sought
All NSCLC							
Niho et al., 2004[11] Phase II	37 pts 61 (44-74) 35% F	Adeno n = 27 Squamous n = 3 Large cell n = 7	IIIB: n = 3 IV: n = 34	0: n = 14 1: n = 23	NR	Gefitinib 250 mg	Response Toxicity
Giaccone et al., 2005[12] Phase II	53 pts 61 (NR) 62%F	Adeno n = 23 Squamous n = 9 BAC n = 6 Large cell n = 8 Other n = 7	NR	NR	Current: n = 10 Former: n = 25 Never: n = 18	Erlotinib 150 mg	Response Survival TTP Safety
Kasahara et al., 2005[13] Phase II	30 pts 64 (44-87) 40%F	Adeno n=25 Squamous n-3 Large cell n=2	IIIb n=4 IV n=26	0: n=20 1: n= 6 2: n= 4	Yes n=20 No n=10	Gefitinib 250 mg	Response Survival TTP Safety
Suzuki et al., 2005[14] Phase II	34 pts 64 (43-73) 38%F	Adeno n=25 Squamous n=5 Other n=4	IV all	0: n=16 1: n=18	NR	Gefitinib 250 mg	Response QoL Toxicity
Reck et al., 2005[15] Phase II	58 pts 67 (41-84) NR	Adeno n=32 BAC n=10 Squamous n=8 Large cell n=4 Other n=4	NR	0: 10% 1: 66% 2: 24%	Current: 33% Former: 48% Never: 19%	Gefitinib 250 mg	Response PFS Toxicity
D'Addario et al., 2005[16] Phase II	63 pts 62 (39-85) 38%F	Adeno n=31 BAC n=6 Squamous n=17 Large cell n=6 Other n=3	IIIb n=15 IV n=47	0: 57% 1: 43%	Never: n=9	Gefitinib 250 mg	Response Survival
Lee et al., 2005[17] Phase II	55 pts 55 (40-74) 93%F	Adeno n=44 Adeno w/BAC n=11	IIIb n=5 IV n=50	0: n=19 1: n=32 2: n= 3	Never: 100%	Gefitinib 250 mg	Response
BAC							
West et al.,	138 pts*	BAC 100%	NR	PS 0/1: 86%	NR	Gefitinib 500 mg	Response

Table 5. First-line treatment with EGFR-TK Inhibitors (single agent) for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Histology	Stage	PS	Smoking status	EGFR-TK inhibitor dose/day	Outcomes sought
2004[18] Phase II	68 (34-89) 51% F						Survival Predictors
Kris et al., 2004[19] Phase II	69 pts* 65 (33-85) 64% F	Pure BAC 25% Adeno/BAC 74%	NR	KPS $\geq$ 80: 91%	Never: 29%	Erlotinib 150 mg	Response Survival
Elderly							
Jackman et al., 2005[21] Phase II	58 pts 75 (70-91) 47%F	Adeno 39 Adeno/BAC 9 Squamous 7 Large cell 2 NSCLC NOS 19	NR	0: 17% 1: 72% 2: 11%	Current: n = 3 Former: n = 49 Never: n = 6	Erlotinib 150 mg	Survival Response
Poor PS							
Dickson et al., 2004[22] Phase II	25 pts 64 (58-84) 32% F	BAC n = 2 Adeno n = 8 Squamous n = 8 Large cell n = 6 Other n = 1	IIIB: 28% IV: 72%	2: 80% 3: 20%	NR	Gefitinib 250 mg	Feasibility/toxicity Response rate Symptom response

* 26% of patients in both studies had previous chemotherapy

Abbreviations: Adeno = adenocarcinoma; Adeno/BAC = adenocarcinoma with bronchoalveolar carcinoma features; BAC = bronchoalveolar carcinoma; EGFR-TK = epidermal growth factor receptor tyrosine kinase; F = female; LCSS = Lung Cancer Symptom Scale; No. = number; NSCLC = non-small cell lung cancer; NSCLC NOS = non-small cell lung cancer not otherwise specified; PS = performance status; pts = patients; QoL = quality of life

Table 6. Summary of tumor response in studies of first-line treatment with EGFR-TK inhibitors (single agent) for advanced NSCLC

Study ID	Diagnosis (no. of patients) [agent]	Sub-groups	N	Survival from start of treatment		Tumor response				
				Median (months)	1-year (%)	% CR	% PR	% SD	% DP	% NE
All NSCLC										
Niho et al., 2004[11]	NSCLC (37) [Gefitinib]	-	37	-	-	0	27	-	-	-
Giaccone et al., 2005[12]	NSCLC (53) [Erlotinib]	-	53	-	-	2	23	30	32	13
Kasahara et al., 2005[13]	NSCLC (30) [Gefitinib]	-	30	10	43.3	0	33	30	37	-
Suzuki et al., 2005[14]	NSCLC (34) [Gefitinib]	-	34	-	-	0	26	-	-	-
Reck et al., 2005[15]	NSCLC (58) [Gefitinib]	-	58	-	-	2	3	40	48	-
D'Addario et al., 2005[16]	NSCLC (63) [Gefitinib]	-	63	10	-	2	8	27	57	6
Lee et al., 2005[17]	NSCLC (55) [Gefitinib]	-	55	Not reached	76.1	4	57	11	28	-
BAC										
West et al., 2004[18]	NSCLC (138) [Gefitinib]	Chemo-naive	67	12	~50	6	15	-	-	-
		Previous treatment (26%)	21	10	~50	0	10	-	-	-
Kris et al., 2004[19]	NSCLC (69) [Erlotinib]	-	59	Median not reached	58	-	25 (15-38)	-	-	-

Table 6. Summary of tumor response in studies of first-line treatment with EGFR-TK inhibitors (single agent) for advanced NSCLC

Study ID	Diagnosis (no. of patients) [agent]	Sub-groups	N	Survival from start of treatment		Tumor response				
				Median (months)	1-year (%)	% CR	% PR	% SD	% DP	% NE
Elderly										
Jackman et al., 2005[21]	NSCLC (58) [erlotinib]	-	66	11	-	0	12	48	39	-
Poor PS										
Dickson et al., 2004[22]	NSCLC (25) [Gefitinib]	-	18	Median not reached	Follow up < 1 year	-	-	61	39	-

Abbreviations: BAC = bronchoalveolar carcinoma; CR = complete response; DP = disease progression; EGFR-TK = epidermal growth factor receptor tyrosine kinase; NE = not evaluable; NSCLC = non-small cell lung cancer; no. = number; PR = partial response; SD = stable disease

Table 7. Second-line treatment with EGFR-TK inhibitors for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Previous treatments	Histology	Stage	PS	Smoking status	EGFR-TK inhibitor dose/day	Outcomes sought
Phase III								
Shepherd et al., 2005 [25]	731 pts 62 (32-89) 35% F	1 prior chemo: 50% 2 prior chemo: 49% chemo incl plat 92%	Adeno 50% Other 50%	NR	0-1: 65% 2-3: 35%	Never 21% Current or former 73% Unk 5%	Erlotinib 150 mg	Survival, PFS, QoL, response, response duration, toxicity
ISEL press release, 2004 [26]	1692 pts NR NR	NR	NR	NR	NR	NR	Gefitinib 250 mg	Survival
Phase II								
Kris et al., 2003 [29]	216 pts 61 (30-84) 46% F	2 prior chemo: 40% 3 prior chemo: 30% $\geq$ 4 prior chemo: 28%	Adeno 69% Squamous 30%	IIIB: 15% IV: 85%	NR	NR	Gefitinib 250 mg vs. 500 mg	Response: bidimensional; Symptoms: FACT-L; Adverse events: NCI CTC 2.0
Fukuoka et al., 2003 [30]	209 pts 61 (28-85) 29% F	Surgery: 31% XRT: 50% 1 prior chemo: 56% 2 prior chemo: 44% Immuno/hormonal treatment: 4%	Adeno 64% Squamous 24% Large cell 9% Undiff 3%	IIIA: 4% IIIB: 18% IV: 78%	NR	NR	Gefitinib 250 mg (500 mg on day 1)	Response: WHO criteria; Toxicity: NCI CTC; QoL: LCS
Perez-Soler et al., 2004 [31]	57 pts 62 (31-83) 60% F	Surgery: 89% XRT: 74% Immuno/hormonal treatment: 9% 1 prior chemo: 18% 2 prior chemo: 42% $\geq$ 3 prior chemo: 40%	Adeno 61% Squamous 16% Large cell 19% Undiff 4%	IIIB: 16% IV: 84%	NR	NR	Erlotinib 150 mg	1. Response rate 2. SD, duration of response, TTP, overall and 1-yr survival, QoL (EORTC QLQ-C30 v 3.0 & EORTC QLQ-LC13), safety

Table 7. Second-line treatment with EGFR-TK inhibitors for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Previous treatments	Histology	Stage	PS	Smoking status	EGFR-TK inhibitor dose/day	Outcomes sought
Cappuzzo et al., 2004[45]	40 pts 74 (70-88) 18% F	1 prior chemo: 53% 2 prior chemo: 40% $\geq$ 3 prior chemo: 7.5% Chemo included platinum: 48%	Squamous 35% Adeno 45% BAC 10% NSCLC undiff 10%	IIIB: 27.5% IV: 72.5%	0: 25% 1: 67.5% 2: 7.5%	NR	Gefitinib 250 mg	Response: RECIST Toxicity: NCI CTC 2.0
Barlesi et al., 2005[46]	51 pts 60 (38-78) 31%F	2 prior chemo 60% 3 prior chemo 29% $\geq$4 prior chemo 12%	Adeno 47% Squamous 29% Large cell 24%	IIIb 26% IV 74%	0/1 72% $\geq$2 28%	Current or former 100%	Gefitinib dose NR	Survival Response Toxicity
Felip et al., 2005[28]	59 pts 56 (35-78) 29%F	NR	Adeno 49% Large cell 32% Squamous 17% Other 3%	NR	NR	NR	Erlotinib 150 mg	Response Toxicity

Abbreviations: Adeno = adenocarcinoma; BAC = bronchoalveolar carcinoma; chemo = chemotherapy; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module; NCI CTC = National Cancer Institute Common Toxicity Criteria; EGFR-TK = epidermal growth factor receptor tyrosine kinase; F = female; FACT-L = Functional Assessment of Cancer Therapy-Lung; ISEL = Iressa Survival Evaluation in Lung cancer trial; LCS = Lung Cancer Symptom Scale; NCI CTC = National Cancer Institute Common Toxicity Criteria; No. = number; NR = not reported; PFS = progression-free survival; PS = performance status; pts = patients; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTP = time to progression; undiff = undifferentiated; WHO = World Health Organization; XRT = radiation therapy

Table 8. Summary of tumor response in studies of second-line treatment with EGFR-TK inhibitors for advanced NSCLC

Study ID	Diagnosis (no. of patients)	Sub-groups	N	Tumor response				
				% CR	% PR	% SD	% DP	% NE
Phase III								
Shepherd et al., 2004[24,25]	NSCLC (~750)	Placebo Erlotinib	211 427	< 1 1	< 1 8	27 35	57 38	15 18
ISEL press release, 2004[26]	NSCLC (1692)	Placebo Gefitinib	NR NR	- 	- 8.2	Better in drug arm*	Better in drug arm*	-
Phase II								
Kris et al., 2003[29]	NSCLC (216) [Gefitinib]	250-mg dose 500-mg dose	102 114	0 0	12 9	- -	- -	- -
Fukuoka et al., 2003[30]	NSCLC (210) [Gefitinib]	250-mg dose 500-mg dose	104 106	0 1	18.5 18.1	35.9 32.4	40.8 41.9	4.9 6.7
Perez-Soler et al., 2004[31]	NSCLC (57) [Erlotinib]	-	57	3.5	8.8	35.1	49.1	3.5
Cappuzzo et al., 2004[45]	NSCLC (40) [Gefitinib]	-	40	2.5	2.5	45	-	-
Barlesi et al., 2005[46]	NSCLC (51) [Gefitinib]	-	51	0	11.7	58.9	-	-
Felip et al., 2005[28]	NSCLC (59) [Erlotinib]	-	52	0	10	36	48	3

* Quantitative data not reported in available data (AstraZeneca press release on ISEL study).

Abbreviations: CR = complete response; DP = disease progression; EGFR-TK = epidermal growth factor receptor tyrosine kinase; ISEL = Iressa Survival Evaluation in Lung cancer trial; NE = not evaluable; NSCLC = non-small cell lung cancer; no. = number; PR = partial response; SD = stable disease

Table 9. Summary of survival in studies of second-line treatment with EGFR inhibitors for advanced NSCLC

Study ID	Diagnosis (no. of patients)	Sub-groups	Survival from start of treatment			Progression-free survival		
			Median (months)	1-year (%)	HR (95% CI) [p-value]	Median TTP (months)	1-year (%)	HR (95% CI) [p-value]
Phase III								
Shepherd et al., 2004[24,25]	NSCLC (~750)	Placebo Erlotinib	4.7 6.7	22 31	0.70 (0.58-0.85) [p = 0.001]	1.8 2.2	- -	0.61 (0.51-0.74) [p < 0.001]
ISEL press release, 2004[26]	NSCLC (1692)	Placebo - all Gefitinib - all	5.1 5.6	- -	0.89 [p = 0.11]	- -	-	-
		Placebo - adeno Gefitinib - adeno	5.4 6.3	- -	0.83 [p = 0.07]	- -	- -	-
Phase II								
Kris et al., 2003[29]	NSCLC (216) [Gefitinib]	250-mg dose 500-mg dose	7 6	27 25	-	- -	- -	-
Fukuoka et al., 2003[30]	NSCLC (210) [Gefitinib]	250-mg dose 500-mg dose	7.6 8	35 29	-	2.7 2.8	- -	-
Perez-Soler et al., 2004[31]	NSCLC (57) [Erlotinib]	-	8.4	40	-	2.1	-	-
Cappuzzo et al., 2004[45]	NSCLC (40) [Gefitinib]	-	5	-	-	3	-	-
Barlesi et al., 2005[46]	NSCLC (51) [Gefitinib]	-	4	-	-	-	-	-

Abbreviations: adeno = adenocarcinoma; EGFR = epidermal growth factor receptor; HR = hazard ratio; ISEL = Iressa Survival Evaluation in Lung cancer trial; no. = number; NSCLC = non-small cell lung cancer; TTP = time to progression

Table 10. Quality-of-life outcomes in patients undergoing second-line treatment for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Treatment (dosage/day)	QoL instrument(s)	QoL outcomes		QoL conclusions
Phase III						
Shepherd et al., 2004[24,25]	731 pts 62 (NR) 35% F	Erlotinib 150 mg	TTDS	TTDS-cough TTDS-dyspnea TTDS-pain	4.9 vs. 3.7 (p = 0.04) 4.7 vs. 2.9 (p = 0.03) 2.8 vs. 1.9 (p = 0.04)	Erlotinib significantly better than placebo for improvement in TTDS-cough, TTDS-dyspnea, and TTDS-pain
Phase II						
Kris et al., 2003[29]	216 pts 61 (30-84) 46%F	Gefitinib 250 mg Gefitinib 500 mg	LCS of FACT-L (improved indicates ≥ 2 point improvement on 28-point scale)		43% improved 35% improved	In both dosage arms, symptom improvement better in PR (96%) vs. SD (73%) vs. PD (17%); adeno vs. other (43% vs. 30%)
Fukuoka et al., 2003[30]	209 pts 61 (28-85) 29% F	Gefitinib 250 mg Gefitinib 500 mg	LCS of FACT-L (improved indicates ≥ 2 point improvement on 28-point scale) TOI FACT-L	LCS-FACT-L 7d TOI q28d FACT-L q28d LCS-FACT-L 7d TOI q28d FACT-L q28d	40.8% 20.9% (11.9 - 32.6) 23.9% (14.3 - 25.9) 37% 17.8% (9.8 - 28.5) 21.9% (13.1 - 33.1)	Gefitinib at either dose associated with measurable improvements compared with baseline in 3 different QoL measures
Perez-Soler, et al., 2004[31]	57 pts 62 (31-83) 60% F	Erlotinib 150 mg	EORTC QLQ-C30 and LC13 administered at baseline, every 2 weeks for 2 months, then every month	Fatigue subscale Dyspnea subscale Cough subscale	67% to 49% 61% to 37% 60% to 39%	Erlotinib associated with measurable improvements compared with baseline in 3 different QoL symptom measures
Comparator studies						
Hanna et al., 2004[32]		Permetrexed Docetaxel	ASBI of LCSS		21.2% (p = NS) 21.5%	Both arms with similar rates of improvement, stabilization, and worsening of symptoms

Table 10. Quality-of-life outcomes in patients undergoing second-line treatment for advanced NSCLC

Study ID	No. of patients, age (median [range]), sex	Treatment (dosage/day)	QoL instrument(s)	QoL outcomes		QoL conclusions
Shepherd et al., 2000[33] as reported in Dancey et al., 2004[47]	204 pts 61 (28-77) 35% F	BSC Docetaxel combined	LCSS	Patient (10 items) Observer (7 items)	Significant difference for 1 (pain) of 17 items	Second-line docetaxel therapy for advanced NSCLC shows a trend (not statistically significant) towards less deterioration in QoL compared with BSC (in this trial that showed a statistically significant survival benefit)
		BSC Docetaxel combined	EORTC QLQ-C30 instrument with the LC13 lung cancer module	Pain/PF/GH	-19/-27/-27 -12/-19/-21 (change in subscale scores for pain/PF/GH)	

Abbreviations: ASBI = Average Symptom Burden Index; BSC = best supportive care; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-L = Functional Assessment of Cancer Therapy-Lung; GH = general health subscale; LCS or LCSS = Lung Cancer Symptom Scale; PF = physical functioning subscale

Table 11. Summary of survival in second-line (or higher) treatment with cytotoxic chemotherapy for advanced NSCLC

Study ID	Diagnosis (no. of patients)	Sub-groups	Survival from start of treatment			Progression-free survival		
			Median (months)	1-year (%)	HR (95% CI) [p-value]	Median TTP (months)	1-year (%)	HR (95% CI) [p-value]
Phase III								
Shepherd et al., 2000[33]	NSCLC (204)	BSC	4.6	-		-	-	
		Docetaxel 75 mg/m^2	7.5	-	p = 0.010	-	-	-
		Docetaxel 100 mg/m^2	5.9	-	p = 0.047	-	-	-
Fossella et al., 2000[34]	NSCLC (358)	Vinorelbine 30 mg/m^2 or ifosfamide 2 mg/m^2	5.4	10		7.9*	-	
		Docetaxel 75 mg/m^2	5.8	32	p = 0.001	8.5*	-	p = 0.093
		Docetaxel 100 mg/m^2	6.6	32	p = 0.002	8.4*	-	p = 0.046
Hanna et al., 2004[32]	NSCLC (571)	Pemetrexed 500 mg/m^2	8.3	30	0.99	2.9	-	0.97
		Docetaxel 75 mg/m^2	7.9	30		2.9	-	[p = 0.76]
Retrospective								
Massarelli et al., 2003[35]	NSCLC 43 pts	Various regimens 3rd line	5.4	-	-	-	-	-
	14 pts	4th line	5.9	-	-	-	-	

*Fossella et al. (2000)[34] reported time to progression (TTP) in patients who were censored at the time of administration of subsequent therapy, which is why the TTP is longer than median survival.

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; no. = number; NR = not reported; NSCLS = non-small cell lung cancer; TTP = time to progression

Table 12. Percentages of patients reporting adverse events by treatment, dose, and grade*

	Gefitinib single-agent				Gefitinib combined with chemotherapy				Erlotinib[†]		Cytotoxic chemotherapy[‡]	
	500 mg/day		250 mg/day		500 mg/day		250 mg/day		150 mg/day			
Adverse event	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**
Skin												
Rash	62-70	5-7	46-60	0-2	44-62	12-13	41-56	3-4	65-67	2-9	5-13	1
Acne	12	2	13	0	22	5	20	1	-	-	-	-
Pruritus	35	1	30	0	11-18	2	8-14	0-1	32	4	-	-
Digestive												
Diarrhea	51-70	5-7	8-56	0-6	39-44	12-25	25-48	4-10	49-54	1-6	21-34	2-4
Anorexia	18	1	6-10	0-4	5-11	1-2	5-6	1	20	4	-	-
Nausea/vomiting	-	-	19	2-9	-	-	-	-	22	3	-	-
Nausea	-	-	3-22	0-1	15	4	15-17	2-3	25	0	15-32	2-6
Vomiting	20	-	6-13	-	10-12	3-5	10-11	2-3	20	0	11-25	1-7
Stomatitis	-	-	-	-	-	-	-	-	16	<1-2	16-34	1-4
Hematologic												
Anemia	-	-	9-12	2	3-6	1-3	2-6	1-2	-	-	-	4-16
Neutropenia	-	-	2-3	-	-	5-6	-	6-7	-	-	-	31-86
Thrombocytopenia	-	-	4	-	-	-	-	-	-	-	-	1-2
Metabolic												
Hypertransaminasemia	18-20	3-6	2-12	0-6	-	-	-	-	-	0	1-8	0-2
Neurological												
Alteration to CNS and PNS	-	-	4	1	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	-	11	0	-	-
Neuropathy	-	-	-	-	3	1	5	1	-	-	-	-
Neuromotor	-	-	-	-	-	-	-	-	-	-	12-15	1-4
Neurosensory	-	-	-	-	-	-	-	-	-	-	16-18	20-37
Whole body												
Fatigue	-	-	6	-	-	-	-	-	25-60	4-19	29	5
Pain	16	-	10	-	-	-	-	-	12	2	-	-
Asthenia	8	1	6-7	0-2	9	2	8-13	1-2			19-41	11-28
Anxiety	-	-	-	-	-	-	-	-	18	4	-	-
Insomnia	-	-	-	-	-	-	-	-	10	2	-	-

Table 12. Percentages of patients reporting adverse events by treatment, dose, and grade*

Adverse event	Gefitinib single-agent				Gefitinib combined with chemotherapy				Erlotinib[†]		Cytotoxic chemotherapy[‡]	
	500 mg/day		250 mg/day		500 mg/day		250 mg/day		150 mg/day			
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4
Weight loss	-	-	1	-	-	-	-	-	12	0	-	-
Dehydration	-	-	-	-	5	5	2	2	3	3-4	-	-
Pulmonary											16-20	20-37
Dyspnea	-	-	-	-	-	-	-	-	17	4	-	-
Cough	-	-	-	-	-	-	-	-	16	0	-	-
Pneumonitis or pulmonary infiltrates	-	-	-	-	-	-	-	-	3	<1	-	-
Musculoskeletal												
Arthralgia	-	-	-	-	-	-	-	-	14	0	-	-
Ocular									27	1		
Conjunctivitis	-	-	1.3	-	5-6	0-1	1-5	0-1	-	-	-	-
Infection	-	-	-	-	-	-	-	-	32	2	16-25	5-14
Cardiac	-	-	-	-	-	-	-	-	-	-	7-12	2-4

*Cells show single value if only one study contributed data, and a range if more than one study contributed data.

[†]Data on erlotinib are from Perez-Soler et al. (2004),[31] Shepherd et al. (2005)[25], and Jackman et al. (2005)[21]

[‡]Chemotherapy studies include studies of docetaxel 75 mg[32-34] and 100 mg;[33,34] venlafaxine or ifosfamide;[34] and pemetrexed.[32]

Abbreviations: CNS = central nervous system; Gr = grade; PNS = peripheral nervous system

Table 13. Patient characteristics predictive of survival, TTP, or response among EGFR inhibitor studies

Characteristic	Favorable prognostic factor	No. of studies indicating an association with response	References	No. of studies indicating an association with survival	References
Sex	Female vs. male	7/13	13,25,29-31,38,48-54	4/7	18,25,38,55-58
Performance status	PS 0/1 vs. PS 2 or KPS $\geq$ 80 vs. $\leq$ 70	1/7	13,25,29,30,53,59,60	10/11	6,7,25,31,54,56,57,61-63
Smoking status	Never vs. former/current	11/15	13,19,25,38,48-53,60,63-66	6/7	8,25,26,38,61,65,67
Prior chemo	Yes vs. no *or* number of prior regimens	1/6	29,31,52,53,59,66	-	-
Age	> 70 vs. $\leq$ 70 years	2/6	25,29,31,60,66,68	0/2	25,68
Rash	Any vs. none	0/3	31,38,48	7/8	6,18,31,38,46,57,62,69
Stage of disease	IIIB vs. IV	0/3	13,31,59	1/1	55
	I-IV vs. recurrent	0/1	60	-	-
Ethnicity	East Asian vs. non-East Asian	2/3	25,30,66	3/3	25,26,55
Prior immuno/hormonal therapy	Yes vs. none	1/1	30	-	-
Hypertransaminasemia		1/1	38	1/1	38
Bone or liver metastasis		0/1	53	2/2	6,7
Pulmonary metastases	> 6 vs. $\leq$ 6	1/1	64	-	-
Brain metastases		0/1	60	-	-
Prior XRT to chest	No vs. yes	1/1	38	-	-
Prior cisplatin or carboplatin	Yes vs. no	0/2	25,53	0/1	25
Prior docetaxel	Yes vs. no	0/1	53	-	-
Time since last chemo	< 6 vs. $\geq$ 6 mo	1/1	31	-	-
Time since diagnosis	-	0/1	29	1/1	31
Weight loss	-	-	-	2/2	6,7
Diarrhea	-	-	-	1/1	38

Abbreviations: chemo = chemotherapy; EGFR = epidermal growth factor receptor; KPS = Karnofsky performance status; No. = number; PS = performance status; TTP = time to progression; XRT = radiation therapy

Table 14. Tumor characteristics predictive of response or survival among EGFR-TK inhibitor studies*

Characteristic	Favorable prognostic factor	No. of studies indicating an association with response	References	No. of studies indicating an association with survival	References
Histologic type	Adeno vs. non-adeno	10/17	13,25,29,42,48,49,70	4/4	25,38,42,57
	BAC vs. non-BAC	2/4	50,71		
	Adeno/BAC vs. adeno, non-BAC vs. other	2/2	53,56	1/1	56
	Papillary vs. non-papillary	1/1	72	1/1	72
Grade	Well/moderately vs. poorly differentiated			2/2	54,73
Stromal invasion				1/1	73
Mucin production				1/1	73
Expression by IHC EGFR	Low vs. high	4/12	25,31,50,52,65,72,74-79	3/4	25,50,73,74
HER2/erbB2	2+/3+ vs. 0/1+	2/6	50,65,70,72,78,80	1/2	73,80
p-EGFR	-	0/4	52,65,72,76	0/1	81
p-Akt status	Positive vs. negative	2/6	50-52,63,65,78	1/3	50,67,70
p-Erk/p-MAPK	2+/3+ vs. 0/1+	3/6	50-52,63,65,76	1/1	73
p-STAT3		0/1	52		
P53		0/1	78		
Ki-67		1/1	65	2/2	65,73
CYFRA 21-1	> 3.5 ng/ml vs. ≤ 3.5 ng/ml	-		1/2	46,67

Table 14. Tumor characteristics predictive of response or survival among EGFR-TK inhibitor studies*

Characteristic	Favorable prognostic factor	No. of studies indicating an association with response	References	No. of studies indicating an association with survival	References
EGFR mutation	Mutation vs. wild type	19/23	13,21,42,48-51,66,70,82-93	7/11	13,42,50,66,67,70,87,89,92,93
KRAS mutation	Mutation vs. Wild type	1/3	21,36,89	0/2	89,94

*Results of multivariable analysis reported in preference to results of univariable analyses when both were available.

Abbreviations: Adeno = adenocarcinoma; Adeno/BAC = adenocarcinoma with bronchoalveolar carcinoma features; BAC = bronchoalveolar carcinoma; EGFR = epidermal growth factor receptor; EGFR-TK = epidermal growth factor receptor tyrosine kinase; IHC = immuno histochemistry; No. = number

Table 15. Association with response for selected predictors

Predictor (reference group)	Study	Reference group response	Comparison group response	Relative risk (95% CI)
Sex				
(women vs. men)	Kris et al., 2003[29]	18/93	4/123	6.0 (2.1 - 17)
	Fukuoku et al., 2003[30]	19/62	18/148	2.6 (1.2 - 5.9)
	Perez-Soler et al., 2004 [31]	NR	NR	NR
	Takano et al., 2004[38]	17/32	15/66	2.3 (1.3 - 4.1)
	Han et al., 2005[51]	5/24	5/49	2.0 (0.7 - 6.4)
	Miller et al., 2004[8]	17/91	4/48	2.2 (0.8 - 6.3)
	Han et al., 2005[52]	NR	NR	NR
	Matsuura et al., 2004[54]	NR	NR	NR
	Kasahara et al., 2005[13]	6/12	4/18	2.2 (0.80 – 6.3)
	Kim et al., 2005[48]	8/19	12/61	2.0 (0.97 – 4.3)
	Mitsudomi et al, 2005[49]	15/23	11/27	2.1 (0.93 – 2.8)
	Tsao et al., 2005[42]	21/146	17/281	2.3 (1.3 – 4.4)
Smoking (never vs. current/former)	Kris et al., 2004[19]	7/19	8/40	1.8 (0.78 - 4.3)
	Han et al., 2005[51]	7/32	3/41	3.0 (0.84 - 10)
	Hotta et al., 2004[60]	7/28	8/28	0.88 (0.37 - 2.1)
	Miller et al., 2004[53]	13/36	8/103	4.6 (2.1 -10)
	Takano et al., 2004[38]	20/32	12/60	3.1 (1.8 - 5.5)
	Han et al., 2005[52]	NR	NR	NR

Table 15. Association with response for selected predictors

Predictor (reference group)	Study	Reference group response	Comparison group response	Relative risk (95% CI)
	Cappuzzo et al., 2004[63]	NR	NR	NR
	Kasahara et al., 2005[13]	5/10	5/20	2.0 (0.75 – 5.3)
	Kim et al., 2005[48]	10/17	10/63	3.7 (1.9 – 7.4)
	Kishi et al., 2005[65]	NR	NR	P=0.0006
	Mitsudomi et al, 2005[49]	17/25	9/25	1.9 (1.0 – 3.4)
	Taron et al., 2005[66]	NR	NR	P<0.05
	Tsao et al., 2005[42]	23/93	12/311	6.4 (3.3 – 12)
	Villaflor et al., 2005[70]	7/20	5/130	9.1 (3.2 – 26)

*As reported from final adjusted model.

Abbreviations: CI = confidence interval; NR = not reported; OR = odds ratio; PS = performance status

Table 16. Association of EGFR mutation with response to gefitinib

Study name	Direction	Responses / Total Mutation	Responses / Total Wild type	Statistics for each study Risk ratio	Lower limit	Upper limit	p-value
Paez et al. 2004[84]	Case-control	5 / 5	0 / 4	9.2	0.7	128.5	0.1001
Jackman et al. 2005[21]	Cohort	3 / 5	2 / 23	6.9	1.5	31.1	0.0119
Kim et al. 2005[48]	Cohort	6 / 6	2 / 21	8.2	2.5	26.7	0.0005
Pao et al. 2004[83]	Case-control	7 / 7	3 / 8	2.4	1.0	5.6	0.0397
Huang et al. 2004[85]	Case-control	7 / 8	2 / 8	3.5	1.0	12.0	0.0456
Lynch et al. 2004[82]	Case-control	8 / 8	1 / 8	5.7	1.3	24.6	0.0207
Kawada et al. 2005[90]	Cohort	8 / 8	1 / 13	8.8	1.9	40.3	0.0050
Tokumo et al. 2005[86]	Case-control	8 / 9	2 / 12	5.3	1.5	19.3	0.0107
Cortes-Funes et al. 2005[87]	Cohort	8 / 10	6 / 73	9.7	4.3	22.3	0.0000
Fujiwara et al. 2005[95]	Cohort	7 / 11	3 / 15	3.2	1.1	9.6	0.0403
Kris et al. 2005[91]	Cohort	10 / 13	3 / 37	9.5	3.1	29.2	0.0001
Han et al. 2005 (2)[89]	Cohort	8 / 13	6 / 46	4.7	2.0	11.2	0.0004
Lynch (IDEAL) 2005[92]	Cohort	6 / 13	6 / 61	4.7	1.8	12.3	0.0016
Kasahara et al. 2005[13]	Cohort	12 / 14	4 / 13	2.8	1.2	6.5	0.0172
Villaflor et al. 2005[70]	Cohort	9 / 14	3 / 44	9.4	3.0	30.1	0.0002
Taron et al. 2005[66]	Cohort	16 / 17	6 / 51	8.0	3.7	17.1	0.0000
Han et al. 2005[51]	Cohort	11 / 17	10 / 73	4.7	2.4	9.3	0.0000
Lynch (INTACT) 2005[92]	Cohort	13 / 18	84 / 152	1.3	0.9	1.8	0.1014
Tsao (BR.21) 2005[42]	Cohort	3 / 19	6 / 81	2.1	0.6	7.8	0.2512
Mitsudomi et al. 2005[49]q	Cohort	24 / 29	2 / 21	8.7	2.3	32.8	0.0014
Tsai et al. 2005[93]	Cohort	22 / 29	10 / 25	1.9	1.1	3.2	0.0163
Takano et al. 2005[50]	Cohort	33 / 39	3 / 27	7.6	2.6	22.3	0.0002

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Appendix A:
MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1966 to September Week 3 2004>
Search Strategy:
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1   (gefitinib or erlotinib or iressa or tarceva or lapatinib or ekb-569 or ci-1033 or zd1839 or osi-774).mp. (817)
2   exp lung neoplasms/ or carcinoma, non-small-cell lung/ (96461)
3   1 and 2 (339)
4   randomized controlled trial.pt. (194192)
5   controlled clinical trial.pt. (67292)
6   Randomized Controlled Trials/ (34359)
7   Random Allocation/ (51911)
8   Double-Blind Method/ (79820)
9   Single-Blind Method/ (8433)
10   or/4-9 (329367)
11   Animal/ not Human/ (2838957)
12   10 not 11 (311915)
13   clinical trial.pt. (392148)
14   exp Clinical Trials/ (159166)
15   (clinic$ adj25 trial$).tw. (103424)
16   ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (76365)
17   Placebos/ (23320)
18   placebo$.tw. (86217)
19   random$.tw. (294378)
20   Research Design/ (38965)
21   (latin adj square).tw. (2126)
22   or/13-21 (693867)
23   22 not 11 (643785)
24   23 not 12 (342333)
25   Comparative Study/ (1152523)
26   exp Evaluation Studies/ (499768)
27   Follow-Up Studies/ (288858)
28   Prospective Studies/ (178265)
29   (control$ or prospectiv$ or volunteer$).tw. (1483791)
30   Cross-Over Studies/ (15073)
31   or/25-30 (2964552)
32   31 not 11 (2271429)
33   32 not (12 or 24) (1817997)
34   12 or 24 or 33 (2472245)
35   3 and 34 (241)
36   limit 35 to english language (216)

Appendix B:
Quality Criteria

Quality criteria for assessment of experimental studies
1. Was the assignment to the treatment groups random?
      Adequate approaches to sequence generation
      - Computer-generated random numbers
      - Random numbers tables
      Inadequate approaches to sequence generation
      - Use of alternation, case record numbers, birth dates or weekdays
2. Was the treatment allocation concealed?
      Adequate approaches to concealment of randomization
      - Centralized or pharmacy-controlled randomization
      - Serially-numbered identical containers
      - On-site computer based system with a randomization sequence that is not
          readable until allocation
      - Other approaches with robust methods to prevent foreknowledge of the
          allocation sequence to clinicians and patients
      Inadequate approaches to concealment of randomization
      - Use of alternation, case record numbers, birth dates or weekdays
      - Open random numbers lists
      - Serially numbered envelopes (even sealed opaque envelopes can be subject to
          manipulation)
3. Were the groups similar at baseline in terms of important prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome
      measure?
9. Did the analyses include an intention to treat analysis?

Quality criteria for assessment of observational studies
From the York CRD handbook (http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Cohort studies
Is there a sufficient description of the groups and the distribution of prognostic factor?
Are the groups assembled at a similar point in their disease progression?
Is the intervention/treatment reliably ascertained?
Were the groups comparable on all-important confounding factors?
Was there adequate adjustment for the effects of these confounding variables?
Was a dose-response relationship between intervention and outcome demonstrated?
Was outcome assessment blind to exposure status?
Was follow-up long enough for the outcomes to occur?
What proportion of the cohort was followed-up?
Were dropout rates and reasons for dropout similar across intervention and unexposed groups?

Case-control studies
Is the case definition explicit?
Had the disease state of the cases been reliably assessed and validated?
Were the controls randomly selected from the source of population of the cases?
How comparable are the cases and controls with respect to potential confounding factors?
Were interventions and other exposures assessed in the same way for cases and controls?
How was the response rate defined?
Were the non-response rates and reasons for non-response the same in both groups?
Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
Was an appropriate statistical analysis used (matched or unmatched)?

Case series
Is the study based on a representative sample selected from a relevant population?
Are the criteria for inclusion explicit?
Did all individuals enter the survey at a similar point in their disease progression?
Was follow-up long enough for important events to occur?
Were outcomes assessed using objective criteria or was blinding used?
If comparisons of sub-series are being made, was there a sufficient description of the series and the distribution of prognostic factors?