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Impact of Epidermal Growth Factor Receptor and *KRAS* Mutations on Clinical Outcomes in Previously Untreated Non–Small Cell Lung Cancer Patients: Results of an Online Tumor Registry of Clinical Trials

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Abstract

Purpose—The impact of epidermal growth factor receptor (*EGFR*) and *KRAS* genotypes on outcomes with erlotinib or gefitinib therapy continues to be debated. This study combines patient data from five trials in predominantly Western populations to assess the impact of *EGFR* and *KRAS* mutations on first-line therapy with an EGFR–tyrosine kinase inhibitor (TKI) and compare clinical versus molecular predictors of sensitivity.

Experimental Design—Chemotherapy-naïve patients with advanced non–small cell lung cancer and known *EGFR* mutation status treated with erlotinib or gefitinib monotherapy as part of a clinical trial were eligible for inclusion. Patients received daily erlotinib (150 mg) or gefitinib (250 mg) until disease progression or unacceptable toxicity. Data were collected in a password-protected web database. Clinical outcomes were analyzed to look for differences based on *EGFR* and *KRAS* genotypes, as well as clinical characteristics.

Results—Patients (223) from five clinical trials were included. Sensitizing *EGFR* mutations were associated with a 67% response rate, time to progression (TTP) of 11.8 months, and overall survival of 23.9 months. Exon 19 deletions were associated with longer median TTP and overall survival compared with L858R mutations. Wild-type *EGFR* was associated with poorer outcomes (response rate, 3%; TTP, 3.2 months) irrespective of *KRAS* status. No difference in outcome was seen between patients harboring *KRAS* transition versus transversion mutations. *EGFR* genotype was more effective than clinical characteristics at selecting appropriate patients for consideration of first-line therapy with an EGFR-TKI.

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Disclosure of Potential Conflicts of Interest

D.M. Jackman, consultant, Genentech; honoraria, Roche. V.A. Miller, consultant, Genentech. P.A. Janne, consultant, AVEO Pharmaceuticals, Boehringer Ingelheim, Roche; research funding, Pfizer, Genentech; patent holder, Genzyme. G.J. Riely, consultant, Astra Zeneca, Roche. M.I. Gallegos Ruiz, employment, Roche. B.E. Johnson, consultant, patent holder, Genzyme. The other authors report no conflicts of interest.

Conclusion—*EGFR* mutation status is associated with sensitivity to treatment with an EGFR-TKI in patients with advanced non–small cell lung cancer. Patients harboring sensitizing *EGFR* mutations should be considered for first-line erlotinib or gefitinib.

Tyrosine kinase inhibitors (TKI) of the epidermal growth factor receptor (EGFR) have become an important therapeutic option for patients with advanced non–small cell lung cancer worldwide. Considerable effort has been directed toward identification of clinical and molecular markers predictive of response, prolonged time to progression (TTP), and longer overall survival (OS) for patients treated with erlotinib and gefitinib. To date, the clinical variables identified include female sex, Asian ethnicity, adenocarcinoma histology, and never-smoking status (1–4). Efforts to identify a predictive biomarker have focused on the EGFR and have included detection of the receptor by immunohistochemical testing, assessment of DNA copy number, and detection of mutations in *EGFR* and *KRAS* (4–11). In clinical trials of first-line therapy with erlotinib or gefitinib across the globe, the most commonly studied and reported biomarker has been the presence or absence of *EGFR* mutations. Our study has focused on this biomarker to allow for pooling of multiple clinical trials and to enable future comparison of outcomes between Asian patients and those from the United States and Europe.

Mutations in *EGFR* and *KRAS* have emerged as promising biomarkers for response to EGFR-TKI therapy. Although two randomized trials comparing an EGFR-TKI with placebo failed to show a clear relationship between *EGFR* mutations and benefit to EGFR-TKI therapy in patients who had progressed after one or two prior regimens (12, 13), preliminary results of the more recent Iressa Pan-Asia Study show improved progression-free survival with first-line gefitinib rather than platinum-based chemotherapy in Asian patients harboring a sensitizing *EGFR* mutation (14). Given the debate, it is important to try to gain information from existing and ongoing trials, particularly in patients from the United States and Europe, to determine the clinical significance of *EGFR* genotype in first-line therapy decisions and to explore any ethnic variation in response to EGFR-TKI therapy. There are currently no published randomized trials of EGFR-TKIs versus combination chemotherapy in previously untreated patients from the United States and Europe. To explore the potential impact of *EGFR* and *KRAS* genotypes on clinical outcomes of chemotherapy-naïve Western patients with non–small cell lung cancer treated with an EGFR-TKI, we pooled data from smaller phase II trials to achieve a more powerful analysis. The study will provide potential insights into the applicability of the findings from the Iressa Pan-Asia Study for previously untreated patients with sensitizing mutations of the *EGFR* to our Western populations.

We established a web-based registry of clinical trials that use EGFR-TKIs in chemotherapy-naïve patients whose tumors were screened for mutations in *EGFR* and *KRAS*. By focusing on trials of first-line EGFR-TKIs, we aimed to eliminate potential modulating effects of prior chemotherapy. This collection of data from several trials enabled us to compare clinical outcomes associated with specific genetic changes (*EGFR* exon 19 deletions versus L858R; *KRAS* transition versus transversion mutations), as well as to assemble more information about less frequently described mutations or combinations of mutations. The study is also intended to compare the impact of clinical versus genomic characteristics in patients treated with an EGFR-TKI. Because only two of the clinical trials of first-line EGFR-TKIs included in our study routinely had collected information about *EGFR* fluorescence *in situ* hybridization status, the role of fluorescence *in situ* hybridization is not addressed in this analysis.

Patients and Methods

Trial and patient eligibility

Clinical trials were eligible for inclusion in this study if they involved prospective administration of gefitinib or erlotinib monotherapy in previously untreated patients with advanced non–small cell lung cancer. All trials were required to have routinely analyzed tumor specimens for *EGFR* mutations. Although *KRAS* analysis was not an eligibility requirement for this study, any available *KRAS* mutation information was included. Investigators from eligible prospective trials were contacted to determine their willingness to contribute individual patient and genotype data to this effort.

All patients had histologically or cytologically confirmed non–small cell lung cancer, stage IV or III-B with a malignant pleural effusion, and had provided written informed consent to treatment and data collection as part of their respective clinical trials. Institutional Review Board approval was obtained from the Dana-Farber/Harvard Cancer Center Institutional Review Board for this analysis. All data was de-identified to assure patient anonymity.

Patient treatment and data collection

Information on race, ethnicity, and smoking status was collected as part of each clinical trial. Patients were classified as never smokers if they had smoked <100 cigarettes and as former smokers if they had quit at least 1 y before enrollment. Two trials did not capture information about pack-years smoked nor differentiate between current versus former smokers (15, 16). Baseline performance status was determined by the treating physician at the time of initial patient enrollment.

Patients were treated with recommended doses of either erlotinib 150 mg daily or gefitinib 250 mg daily. Dose reductions and delays were permitted as per each trial protocol (7, 15–18). Patients were treated until development of progression or unacceptable toxicity. Patients underwent planned radiologic staging assessments at baseline and then every 6 to 8 wk while on therapy. In each of the included clinical trials, Response Evaluation Criteria in Solid Tumors criteria were used to determine radiologic response, stability, or progression. There was no central radiologic or pathologic review for the cases included in this study.

EGFR and *KRAS* mutation testing

Mutation detection was done in each of the five included trials with the use of well-established methods of direct DNA sequencing of exons 18 to 21 of the *EGFR,* and exons 1 and 2 of *KRAS* (19–22). In two of the trials (15, 17, 18), samples that were insufficient for direct sequencing or whose results on direct sequencing were indeterminate were then screened for mutations with the use of Surveyor DNA endonuclease combined with the WAVE HS high-performance liquid chromatography system as previously published (Transgenomic, Inc.; ref. 23). This platform was also used to verify the mutation status of patients in one of the trials in which primary testing had not been done at our center (15).

Statistical analysis

The response rate and disease control rate (percentage of response plus stable disease) were calculated. OS and TTP were measured from the start of TKI, and were analyzed by Kaplan-Meier estimates and log-rank testing. The proportional hazards model was used for multivariate analysis to assess the independent effects of different mutations and to obtain their hazard ratio estimates. Statistical calculations were done with the use of the SPSS statistical package (SPCC Inc.). All *P*-values were two-sided.

Clinical outcomes (response, TTP, and OS) were determined for all patients with known sensitizing mutations in the EGFR. Known sensitizing mutations included deletions in exon 19; point mutations L858R, L861Q, and G719X; and duplications in exon 19. In addition, specific subsets (exon 19 deletion versus L858R mutations, erlotinib-treated versus gefitinib-treated patients) were analyzed to look for potential differences in outcome based on genotype.

In a separate analysis, patients with complete information on potential clinical predictors (gender, race, smoking history, and histology) were divided into two clinical subsets: those with 3 or 4 clinical predictors, and those with ≤2 clinical predictors. Outcomes of therapy (response rate, TTP, OS) were compared between the two groups and by *EGFR* mutation status. The predictive abilities of *EGFR* mutation status and clinical predictors were assessed by the c-index, which is a rank correlation measure of concordance between the predicted probabilities or risks, and observed data. The c-index for response rate was computed by the logistic regression procedure in SAS 9.1 (SAS Institute Inc.), whereas the rcorr.cens function in the Hmisc package was used in R 2.6.2 for the analysis of TTP and OS.

Results

Patient characteristics

At the time of analysis, there were six eligible trials of first-line treatment with erlotinib or gefitinib monotherapy in predominantly Western populations in which *EGFR* mutations were systematically studied; our study includes five of these clinical trials (Table 1; refs. 7, 15, 17, 18, 24). *EGFR* mutation analysis has not yet been completed in the sixth trial, so that trial has not yet been incorporated into the database (25).

Between March 2003 and July 2008, a total of 317 chemotherapy-naïve patients were treated with erlotinib or gefitinib in one of these five trials. Four of the five trials have been published in peer-reviewed journals. The fifth has completed accrual, and has been presented at national and international meetings. Of these, tumor specimens from 223 patients had undergone successful mutation testing for *EGFR* and/or *KRAS*. The remaining patients have not undergone mutation testing due to inadequate or insufficient tissue available. Demographic and outcomes data were collected on those patients whose *EGFR* mutation status has been determined. Baseline patient characteristics are listed in Table 2. The majority of patients were Caucasian (95%) and female (69%); one third of patients had never smoked. Eighty-six percent of patients had tumors with adenocarcinoma histology, with 35% of these patients exhibiting bronchioloalveolar carcinoma features. This histologic distribution reflects, in part, the eligibility criteria for two of the trials: one required adenocarcinoma histology, whereas another required adenocarcinoma with bronchioloalveolar carcinoma features. Eighty-six percent received erlotinib, whereas 14% received gefitinib.

The median potential follow-up was 55.9 months. At the time of analysis, 46 patients were known to be still alive, 143 have died, and another 34 patients were censored. Nine patients were known to be progression-free on continuing therapy with an EGFR inhibitor.

EGFR mutations

Within this study, tumors from 84 patients were found to harbor a sensitizing mutation in *EGFR* in the absence of any concomitant known resistance mutation. The majority of patients were women (81%), had adenocarcinoma histology (89%), and had no history of tobacco use (58%). Ninety percent of the *EGFR*-mutant patients in this study were Caucasian.

Of the 84 patients harboring a sensitizing *EGFR* mutation who were treated with either erlotinib or gefitinib, 56 patients (67%) achieved an objective response (1 complete response, 55 partial response). The disease control rate (responses plus stable disease) was 96%, with two patients not evaluable for response and one patient developing rapid disease progression. As previously described (16), the patient with unexpected progressive disease was a 42-year-old man with an exon 19 deletion and *de novo MET* amplification, which has been associated with resistance to gefitinib and erlotinib (26, 27).

The 84 patients with sensitizing *EGFR* mutations had a median TTP of 11.8 months (95% confidence interval, 9.3–14.6 months), with a median OS of 23.9 months (95% confidence interval, 19.5–34.4 months). Patients with exon 19 deletions had a longer median TTP (14.6 versus 9.7 months; $P = 0.02$) and OS (30.8 versus 14.8 mo; $P < 0.001$) compared with those harboring the L858R mutation (Fig. 1A). Response rates were not significantly different between exon 19 deletions and L858R mutations (63% versus 50%; $P = 0.39$).

Outcomes of the 84 patients with known sensitizing mutations were also compared by drug-given erlotinib ($n = 56$) versus gefitinib ($n = 28$). There were no statistically significant differences in response rate (erlotinib, 70%; gefitinib, 60%; $P = 0.47$), median TTP (erlotinib, 13.0 months; gefitinib, 11.4 months; $P = 0.49$), and median OS (erlotinib, 28.7 months; gefitinib, 20.8 months; $P = 0.10$).

Role of clinical predictors

Patients were divided into two groups based on four major clinical predictors (race, gender, smoking status, and tumor histology): those with 3 or 4 clinical predictors versus those with ≤2 (Fig. 2). Such a clinical distinction did indeed help to select a subset of clinically enriched patients with an increased likelihood of response (49% versus 20%; $P < 0.001$) and prolonged median TTP (9.1 versus 4.4 months; $P = 0.0165$).

Although clinical predictors showed some value in selecting patients for first-line EGFR-TKI therapy, further analyses show *EGFR* mutation status was a better predictor of outcome. Within the high clinical prediction group (3 or 4 clinical predictors), *EGFR* mutation status was able to divide these 59 patients into two clear subsets: the 38 patients with sensitizing mutations (response rate, 76%; TTP, 12.9 months) and the 21 patients without a sensitizing mutation (response rate, 0; TTP, 1.8 months). Within the low clinical prediction group (0–2 clinical predictors), patients had a wide range of outcomes, and *EGFR* mutation status was again able to determine more clearly who would benefit: those with an EGFR mutation had improved response rate (59% versus 4%; $P < 0.001$), prolonged median TTP (10.8 versus 2.5 months; $P < 0.0001$), and longer median OS (24.5 versus 11.8 months; $P = 0.002$) compared with those with wild-type *EGFR*. When similar analyses were done with the use of stricter (patients with all four clinical predictors) or looser (patients with ≥2 clinical predictors) criteria, the impact of *EGFR* genotype was similar.

Logistic regression models of response resulted in a c-index of 0.87 for *EGFR* mutation status and 0.65 for clinical predictors. The predictive ability was not as strong for TTP in general, with a c-index of 0.68 for *EGFR* mutation status and 0.55 for clinical predictors.

For the OS outcome, the c-index was 0.61 for *EGFR* mutation status and 0.54 for clinical predictors. Overall, we conclude that *EGFR* mutation status yields consistently a higher predictive ability than the clinical predictors.

Impact of EGFR and KRAS mutations on clinical outcomes

There were 175 patients with complete information on both *EGFR* and *KRAS* genotypes. Four of these patients were excluded from analysis due to the presence of a known non-

KRAS resistance mutation (one exon 20 insertion, one T790M), or due to concomitant *EGFR* and *KRAS* mutations (two patients). Outcomes for these patients are reported separately. The remaining 171 patients were categorized into three groups: (*a*) sensitizing *EGFR* mutation but *KRAS* wild-type, (*b*) *EGFR* wild-type but *KRAS* mutant, or (*c*) wild-type for both *EGFR* and *KRAS* (Fig. 1B).

Sensitizing *EGFR* mutations were associated with higher response rates, and longer TTP and OS when compared with patients without *EGFR* mutations. The two other patient groups—patients with *KRAS* mutations, and patients who were wild-type for both *EGFR* and *KRAS*—fared similarly: response rate was low (0%–5%), and median TTP was <4 months in each group. Median OS was ~1 year, similar to the estimated survival noted in other trials of patients with metastatic non–small cell lung cancer. These observations were confirmed by multivariate analysis to assess the independent effects of each mutation status on TTP and OS. Compared with patients with sensitizing *EGFR* mutations, the *EGFR* wild-type group had almost four times the risk of progression (hazard ratio, 3.8; $P < 0.001$) and twice the risk of death (hazard ratio, 2.0; $P = 0.004$). In contrast, *KRAS* mutation status was clearly not associated with TTP (hazard ratio, 1.0; $P = 0.955$) or OS (hazard ratio, 1.2; $P = 0.406$).

Further analyses of 39 patients harboring specific *KRAS* mutations revealed differences in the incidence of transition mutations (purine->purine or pyrimidine->pyrimidine) versus transversion mutations (purine->pyrimidine or pyrimidine->purine). *KRAS* mutations in never smokers were more likely to be transitions (7 of 9; 78%), whereas *KRAS* mutations in former or current smokers were more likely to be transversions (21 of 30; 70%; (Fisher's $P = 0.019$), as has been shown previously (28). Information about the specific type of *KRAS* mutation was unavailable in two patients.

Despite differences in patterns of incidence in *KRAS* mutations by smoking status, clinical outcomes were similar between transition or transversion muations: there were no objective responses in either group, and there were no significant differences in TTP (transition 3.3 months versus transversion 1.9 months; $P = 0.24$) or OS (transition 10.2 months, transversion 13.3 months; $P = 0.30$), although the analysis is limited by small sample size.

Patients with rarer or multiple mutations

The genotype and clinical outcomes of patients with rarer mutation or multiple mutations are listed in Table 3. Some of these include mutations known to be associated with sensitivity (L861Q) or resistance (exon 20 insertions) to EGFR-TKI. Other mutations or combinations of mutations, however, occur much less frequently. Of particular note is a patient with both an *EGFR* exon 19 deletion and a *KRAS* mutation; this patient did well with erlotinib therapy, achieving stable disease for 25.8 months.

Discussion

Preliminary results from the Iressa Pan-Asia Study provide evidence that EGFR sensitizing mutations are predictive of longer progression-free survival when treated with gefitinib compared with chemotherapy, potentially sparing a subset of patients from initial therapy with more toxic agents (14). Although our study is not randomized, it does confirm the impressive outcomes with an EGFR-TKI in Western patients with sensitizing *EGFR* mutations compared with *EGFR* wild-type patients receiving an EGFR-TKI. Moreover, our data suggest that patients who are *EGFR* wild-type should be considered for combination chemotherapy rather than an EGFR-TKI in the first-line setting.

Furthermore, in the Western population studied in this trial, specific *EGFR* genotype has an impact. Similar to earlier observations from smaller datasets, exon 19 deletions are

associated with longer TTP and OS when compared with L858R point mutations. A waterfall plot of changes in tumor measurements of indicator lesions from baseline to the time of best response provides a visual depiction of the impact of *EGFR* and *KRAS* genotypes on sensitivity to EGFR-TKI therapy (Fig. 3).

There are several observations from *KRAS* analysis. The genotype of *KRAS* mutations was different in smokers versus nonsmokers, as has been previously observed (28). However, this difference between transition and transversion mutations did not have an impact on the clinical outcome of EGFR-TKI therapy. Secondly, *KRAS* genotype in general did not have a significant independent impact on outcomes of treatment with an EGFR-TKI: patients with *KRAS* mutations were almost uniformly wild-type for *EGFR*, and the *EGFR* wild-type group had low response rate and short TTP across the board, irrespective of *KRAS* mutation status.

This study also shows the potential value of using genomic assessments of *EGFR* rather than using clinical characteristics to select patients for initial treatment with EGFR-TKIs. Whereas the use of clinical characteristics can be helpful in settings in which *EGFR* mutation testing is neither feasible nor available, this study provides evidence that genomic testing is more accurate in selecting a group of patients with increased chance of sensitivity to therapy with an EGFR-TKI. Based on the data presented here, it is appropriate to consider patients with known sensitizing mutations in *EGFR* for first-line therapy with an EGFR-TKI.

Online databases, such as our own, can help to expedite the collection and analysis of patients across multiple centers to allow for more powerful analysis of clinical outcomes associated with specific genotypes. In addition to confirming results that had been seen in smaller series, we look forward to planned collaborations to study differences in the incidence of various genotypic changes and clinical outcomes of therapy with EGFR-TKIs.

Translational Relevance

The impact of epidermal growth factor receptor (*EGFR*) and *KRAS* mutations on clinical outcomes to EGFR–tyrosine kinase inhibitor (TKI) therapy in non–small cell lung cancer remains an area of investigation and debate. Although preliminary data from randomized trials of first-line therapy in Asia have suggested a benefit for gefitinib therapy over cytotoxic chemotherapy in patients with known *EGFR* mutations, no such randomized data yet exist for predominantly Western populations. We have created a database of five clinical trials from the United States and Europe, in which chemotherapy-naïve patients with advanced non–small cell lung cancer were treated with an EGFR-TKI, and *EGFR* status was tested. Based on the findings presented here, clinicians can derive a stronger understanding of the importance of *EGFR* mutation testing rather than clinical characteristics in selecting appropriate patients for first-line EGFR-TKI therapy; moreover, they can get a clearer estimation of the impact of specific changes in *EGFR* and *KRAS* on patient outcomes.

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References

1. Fukuoka M, Yano S, Giaccone G, et al. Multiinstitutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 trial) [corrected]. J Clin Oncol. 2003; 21:2237–2246. [PubMed: 12748244]
2. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA. 2003; 290:2149–2158. [PubMed: 14570950]
3. Perez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. J Clin Oncol. 2004; 22:3238–3247. [PubMed: 15310767]
4. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353:123–132. [PubMed: 16014882]
5. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst. 2005; 97:643–655. [PubMed: 15870435]
6. Hirsch FR, Varella-Garcia M, McCoy J, et al. Increased epidermal growth factor receptor gene copy number detected by fluorescence *in situ* hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group study. J Clin Oncol. 2005; 23:6838–6845. [PubMed: 15998906]
7. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol. 2008; 26:1472–1478. [PubMed: 18349398]
8. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol. 2005; 23:2513–2520. [PubMed: 15738541]
9. Niho S, Kubota K, Goto K, et al. First-line single agent treatment with gefitinib in patients with advanced non-small-cell lung cancer: a phase II study. J Clin Oncol. 2006; 24:64–69. [PubMed: 16382114]
10. Taron M, Ichinose Y, Rosell R, et al. Activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor are associated with improved survival in gefitinib-treated chemorefractory lung adenocarcinomas. Clin Cancer Res. 2005; 11:5878–5885. [PubMed: 16115929]
11. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol. 2006; 24:3340–3346. [PubMed: 16785471]
12. Thatcher N, Chang A, Purvish P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005; 366:1527–1537. [PubMed: 16257339]
13. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med. 2005; 353:133–144. [PubMed: 16014883]
14. Mok, T.; Wu, YL.; Thongprasert, S., et al. Phase III, randomised, open-label, first-line study of gefitinib (G) vs carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) (IPASS). Stockholm, Sweden: 2008.
15. Giaccone G, Gallegos Ruiz M, Le Chevalier T, et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. Clin Cancer Res. 2006; 12:6049–6055. [PubMed: 17062680]
16. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol. 2008; 26:2442–2449. [PubMed: 18458038]
17. Jackman DM, Lindeman N, Lucca J, et al. Phase II study of erlotinib in chemo-naive women with advanced pulmonary adenocarcinoma. J Clin Oncol. 2007; 25 abstract 7591.

18. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol. 2007; 25:760–766. [PubMed: 17228019]

19. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004; 350:2129–2139. [PubMed: 15118073]

20. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004; 101:13306–13311. [PubMed: 15329413]

21. Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med. 2005; 2:e17. [PubMed: 15696205]

22. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004; 304:1497–1500. [PubMed: 15118125]

23. Janne PA, Borras AM, Kuang Y, et al. A rapid and sensitive enzymatic method for epidermal growth factor receptor mutation screening. Clin Cancer Res. 2006; 12:751–758. [PubMed: 16467085]

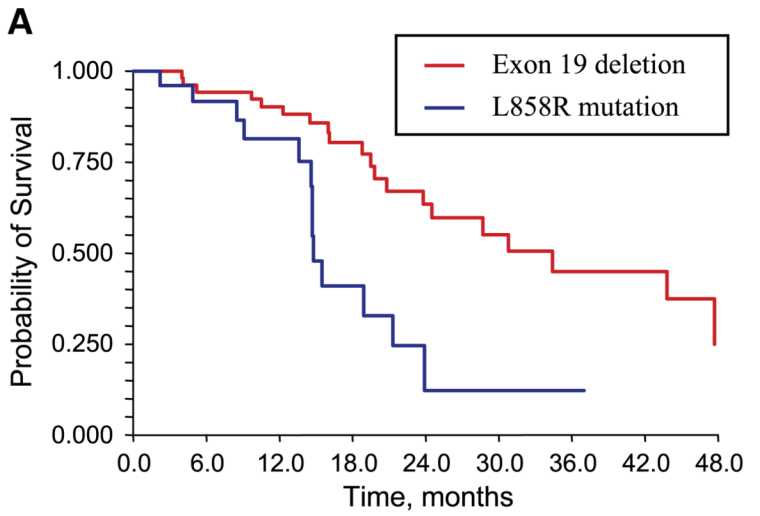
24. Sequist LV, Martins RG, Spigel DR, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. JCO. 2008; 26:2442–2449.

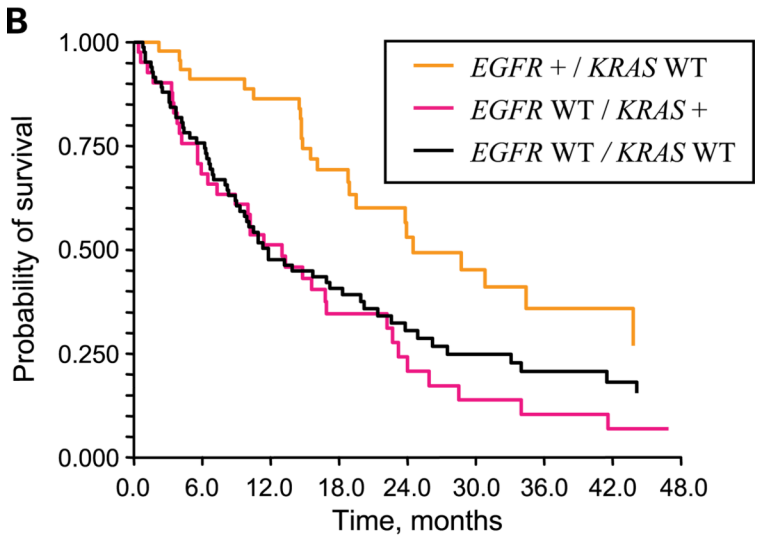
25. West HL, Franklin WA, McCoy J, et al. Gefitinib therapy in advanced bronchioloalveolar carcinoma: Southwest Oncology Group study S0126. JCO. 2006; 24:1807–1813.

26. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. PNAS. 2007; 104:20932–20937. [PubMed: 18093943]

27. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007; 316:1039–1043. [PubMed: 17463250]

28. Riely GJ, Kris MG, Rosenbaum D, et al. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res. 2008; 14:5731–5734. [PubMed: 18794081]





	EGFR + / *KRAS* WT	*EGFR* WT / *KRAS* +	*EGFR* WT / *KRAS* WT	
N	47	41	83	P
RR	68%	0	5%	< .001
Median TTP (months)	13.1	3.3	3.1	< ,0001
Median OS	24.5	13.0	11.8	.002

Fig. 1.

A, OS in patients with exon 19 deletions versus L858R point mutations. *B*, OS based on *EGFR* and *KRAS* status.

Outcomes by number of clinical predictors

	3 + clinical predictors	2 or fewer	p
N	59	164	
RR	29/59 (49%)	32/164 (20%)	<0.001
Median TTP	9.1	4.4	0.0165
Median Survival	20.8	14.7	0.1139

Outcomes of clinically enriched patients by *EGFR* mutation status

	Sensitizing EGFR Mutation	Other	p
N	38	21	
RR	29/38 (76%)	0/21 (0%)	<0.001
Median TTP	12.9	1.8	<0.0001
Median Survival	23.8	14.8	0.0515

Outcomes of clinically unenriched patients by *EGFR* mutation status

	Sensitizing EGFR Mutation	Other	p
N	44	118	
RR	27/46 (59%)	5/118 (4%)	<0.001
Median TTP	10.8	2.5	<0.0001
Median Survival	24.5	11.8	0.0016

Fig. 2.
Comparison of outcomes by clinical enrichment and *EGFR* mutation analysis.

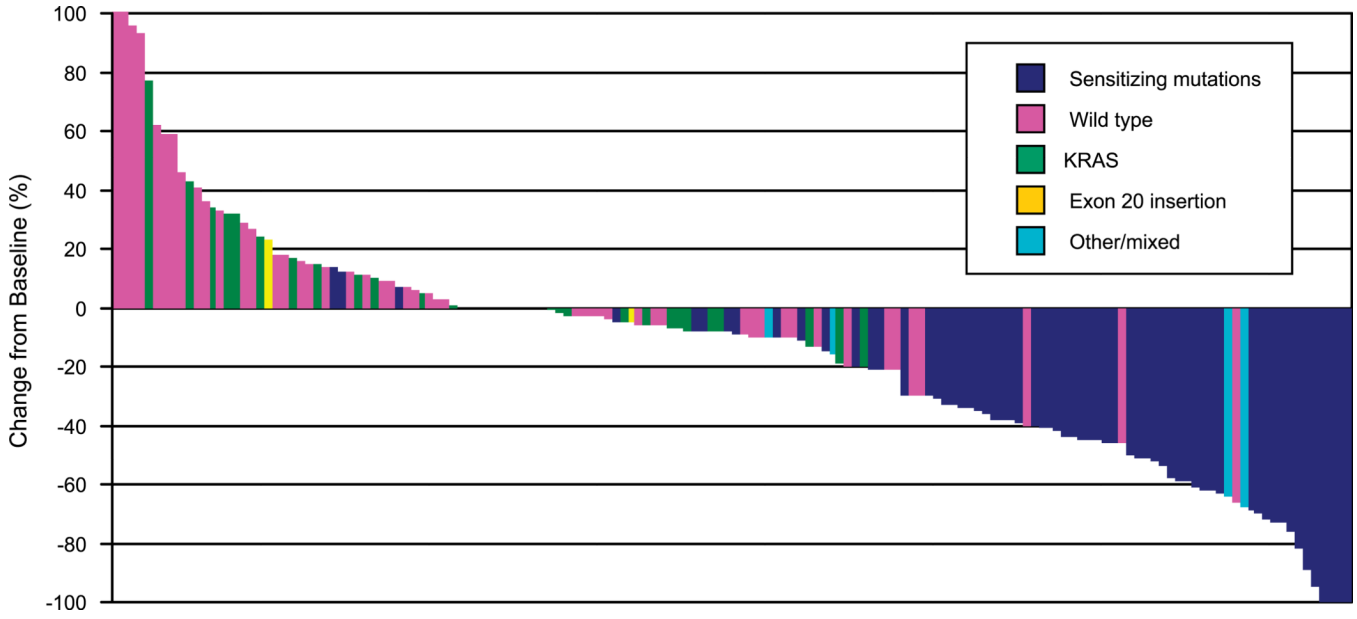


Fig. 3.
Maximal reduction for indicator lesions (Response Evaluation Criteria in Solid Tumors classification) by *EGFR* and *KRAS* genotype.

Table 1

Trials of first-line EGFR-TKI therapy included in this study

Trial/Author	Patient selection	Drug	1st-line pts treated, *n*	1st-line pts tested for *EGFR, n*	1st-line pts tested for *KRAS, n*
Giaccone et al. (1)	Unselected	Erlotinib	53	28	26
Jackman et al. (2)	Patients ≥ age 70 y	Erlotinib	80	43	41
Miller et al. (3)	Adenocarcinoma with BAC features	Erlotinib	75	57	56
Sequist et al. (4)	Known EGFR mutations	Gefitinib	31	31	0
Jackman et al. (5)	Women, adenocarcinoma, not current smokers	Erlotinib	78	63	52

Abbreviations: pts, patients; BAC, bronchioloalveolar carcinoma.

Table 2

Baseline demographic and molecular characteristics of the entire study

Total, *N*	**223**
Age, median (range)	69 (26–91)
Sex, *n* (%)	
Male	70 (31%)
Female	153 (69%)
Race	
Caucasian	212 (95%)
Asian	8 (4%)
Black	3 (1%)
Smoking status	
Never	73 (33%)
Former/Current	150 (67%)
Performance status	
0	48 (22%)
1	158 (71%)
2	16 (7%)
Unreported	1 (<1%)
Histology	
Adenocarcinoma (non-BAC)	113 (51%)
Adenocarcinoma with predominant BAC features	78 (35%)
Other	32 (14%)

NOTE: Percentages may not add up to 100 due to rounding.

Table 3

Clinical outcomes for rare mutations or rare combinations of mutations

Mutation(s)	*N*	Response	TTP, mo	OS, mo
Suspected sensitizing mutation				
L861Q	1	SD	4	8.8
G719A	1	SD	3.9	5.2
Exon 19 duplication	1	PR	22.1+	22.1+
Suspected resistance mutation				
Exon 20 insertion	31	1 SD, 2 PD	1.0 (median)	1.5 (median)
Multiple mutations				
Exon 19 del + L861Q + G873E	1	SD	20.5	34.9+
L858R + T790M	1	PD	1.9	17.5
T790M + KRAS mutation	1	PD	0.8	0.8
Exon 19 del + KRAS mutation	1	SD	25.8	44.7+
V802I + KRAS mutation	1	PD	0.9	4.0
G719A + G779C	1	PR	2.9+	2.9+

Abbreviations: SD, stable disease; PR, partial response; PD, progressive disease.