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Review Article

Overview of Gefitinib in Non-small Cell Lung Cancer: An Asian Perspective

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Clinical experience with the EGFR-TKI gefitinib in Asian patients with NSCLC will be reviewed, both in patients who have previously failed chemotherapy and in the first-line setting (gefitinib is currently not licensed for first-line treatment). Tolerability and specific adverse events in patients of Asian origin will be discussed. Differing objective response rates between patients of Asian and non-Asian origin when treated with gefitinib (and standard cytotoxics) will also be discussed along with EGFR mutations and drug resistance. Reports of Phase II/III clinical experience with gefitinib 250 mg/day in Asia were identified by searching in Medline and ASCO databases for publications between 1993 and 2008. Defined search criteria included (gefitinib OR Iressa OR ZD1839) AND NSCLC AND (Asia OR Japan OR China OR Taiwan OR Korea) or 'Clinical trial' type, with additional searches, including AND 'interstitial lung disease (ILD)' or 'EGFR mutation'. Numerous Phase II/III trials including patients of Asian origin with previously treated advanced NSCLC report a consistent clinical benefit of gefitinib. Gefitinib is generally well tolerated by patients with NSCLC although the incidence of ILD in Japanese patients must be noted. Studies analyzing EGFR mutations indicate that these mutations occur at a much higher rate in patients of Asian origin than in non-Asian patients. Data from several studies indicate that EGFR mutation-positive patients of Asian origin have better efficacy outcomes with first-line gefitinib when compared with those who are EGFR mutation-negative. Research is ongoing to evaluate the role of tailoring patients' treatment according to their genetic phenotype.

Key words: non-small cell lung cancer – gefitinib – Asian patients – EGFR mutations

INTRODUCTION

Lung cancer is a leading cause of mortality worldwide, with ~1.18 million deaths reported every year (1). The incidence of lung cancer in Asia varies depending on the region, with the reported incidence in 2002 ranging from 14.3 per 100 000 in south central Asia to 50.4 in Japan and 61.4 in China (1). Non-small cell lung cancer (NSCLC) comprises ~80% of all lung cancers and patients usually present in the advanced stages, which can result in poor prognosis and difficulty in managing the disease (2).

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is expressed or overexpressed in a variety of tumors, including NSCLC (3,4). High levels of EGFR expression and dysregulation seem to promote tumor growth by increasing cell proliferation, motility, adhesion, invasive capacity and by evading apoptosis and therefore have been associated with poorer prognosis in several studies (5–12). Given the importance of EGFR in tumor biology, EGFR-targeted cancer therapies have been developed, including the orally active, EGFR-tyrosine kinase inhibitor (EGFR-TKI) gefitinib (IRESSA, AstraZeneca). EGFR-TKIs inhibit the intracellular tyrosine kinase domain of the EGFR and therefore block the signal transduction pathways implicated in the proliferation and survival of cancer cells (13,14).

Clinical data and experience in the use of gefitinib is now extensive; as of July 2008, an estimated 290 000 patients

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have been treated with gefitinib (AstraZeneca, data on file), with approximately 135 000 of these patients being of south-east Asian origin. Gefitinib has demonstrated a consistent clinical benefit in patients of Asian ethnicity, with more patients experiencing benefit compared with non-Asian patients (15,16).

This review discusses the use of gefitinib in Asian patients with advanced NSCLC using the extensive clinical data available and also summarizes data on the discovery of the EGFR mutations that suggest an underlying biological basis of the apparent difference in efficacy outcomes between Asian and non-Asian patients. Reports of Phase II/III clinical experience with gefitinib 250 mg/day in Asia were identified by searching with Medline and ASCO abstract databases for publications between 1993 and 2008 using defined search criteria: (gefitinib OR Iressa OR ZD1839) AND NSCLC AND (Asia OR Japan OR China OR Taiwan OR Korea) of 'Clinical trial' type, with additional searches including AND 'interstitial lung disease (ILD)' or 'EGFR mutation'.

GEFITINIB IN PRE-TREATED ADVANCED NSCLC

A number of Phase II and III studies have investigated the efficacy and tolerability of gefitinib in patients with pre-treated advanced NSCLC and a summary of these studies is shown in Table 1 (17–29).

Phase II Studies

Gefitinib was approved for use in pre-treated advanced NSCLC following the results of two Phase II studies of gefitinib 250 and 500 mg/day, IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) 1 and 2 (19,22). These doses were chosen, based on Phase I study results, to maximize the potential for therapeutic activity with an ample safety margin (14,30). In these studies, the 250 mg/day dose was above the lowest dose at which clinical responses were seen, was well tolerated, ensured adequate gefitinib exposure and inhibited EGFR signaling in skin biopsies. The 500 mg/day dose was the highest dose level that was well tolerated for long periods by most patients.

IDEAL 1 was a randomized, double-blind, parallel-group, multicenter Phase II trial, investigating the efficacy and safety of gefitinib 250 and 500 mg/day in 210 patients with advanced NSCLC, who had previously received one or two chemotherapy regimens, recruited at 43 centers in Europe, Australia, South Africa and Japan (19). No significant difference was seen in the response rate to gefitinib 250 or 500 mg/day (18.4 versus 19.0%). The symptom improvement rate was 40.3% for the 250 mg/day group and 37.0% for the 500 mg/day group. Pre-planned analyses indicated that the response rate for the two doses combined was significantly higher in Japanese than non-Japanese patients (27.5 versus 10.4%, $P = 0.0023$). A retrospective analysis of IDEAL 1 showed that in Japanese patients, gefitinib 250 and 500 mg/day were associated with median survivals of 13.8 and 11.2

Table 1. Summary of Phases II and III gefitinib 250 mg/day efficacy data in pre-treated patients with advanced NSCLC[a]

Trial	Phase	Patients (*n*)	Patient origin	Number of patients receiving 250 mg/day	Response rate (%)	TTP/PFS (months)	MST (months)	1-year survival (%)
IDEAL 1 (19)	II	210	World	103	18.4	2.7	7.6	35.0
IDEAL 1 Japanese Subset (26)	II	102	Japan	51	27.5	—	13.8	57.0
IDEAL 2 (22)	II	221	USA	102	12.0	—	7.0	25.0
Taiwanese study (17)	II	36	Taiwan	36	33.3	4.7	9.5	45.1
Chinese study (20)	II	159	China	159	27.0	—	10.0	44.0
SIGN (18)	II	141	World	68	13.2	3.0	7.5	—
ISEL (25)	III	1692	World	1129	8.0	3.0	5.6	27.0
ISEL Asian Subset (27)	III	342	Asia	235	12.4	4.4	9.5	41.0
INTEREST (21)	III	1466	World	733	9.1	2.2	7.6	—
INTEREST Asian Subset (21)	III	314	Asia	154	—	—	10.4	—
V-15-32 (24)	III	489	Japan	245	22.5	2.0	11.5	47.8
ISTANA (23)	III	161	Korea	82	28.1	3.3	—	—
Chiu et al. (28)	II	76	Taiwan	76	33.3	5.0	9.9	—
Wang et al. (29)	II	151	China	151	29.8	12.0	15.3	57.0

[a]Studies shown are Phase II and III studies identified for this review article from the database searches conducted; NSCLC, non-small cell lung cancer; TTP, time to progression; PFS, progression-free survival; MST, median survival time; IDEAL, Ideal Dose Evaluation in Advanced Lung Cancer; SIGN, Second-line Indication of Gefitinib in NSCLC; ISEL, Iressa Survival Evaluation in Lung Cancer; INTEREST, Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere; ISTANA, Iressa as Second-Line Therapy in Advanced NSCLC-Asia.

months, respectively (26), compared with 7.6 and 8.0 months, respectively, in the overall population (19).

IDEAL 2 was a randomized, double-blind, parallel-group, multicenter Phase II trial, investigating the efficacy and safety of oral gefitinib 250 or 500 mg/day in 221 patients from the USA with Stage III or IV NSCLC for which they had received at least two chemotherapy regimens (22). As with IDEAL 1, no significant difference was seen in the response rate to gefitinib 250 or 500 mg/day (12 versus 9%). Median survival was 7 months with gefitinib 250 mg/day and 6 months with gefitinib 500 mg/day and symptom improvement rates were 43 and 35%, respectively.

The 250 mg/day dose of gefitinib was chosen for subsequent trials based on the tolerability and efficacy data observed in the IDEAL trials. Gefitinib was well tolerated and most adverse events (AEs) were mild to moderate in intensity. The most common AEs with gefitinib 250 mg/day were skin rash (reported in 46.6 and 62% of patients in IDEAL 1 and 2, respectively) and diarrhea (reported in 39.8 and 57%, respectively). A similar AE profile was seen with gefitinib 500 mg/day, but there was a higher incidence of Grade 3 and 4 AEs reported.

Other important Phase II studies of gefitinib 250 mg/day have focused specifically on Asian patients with locally advanced or metastatic NSCLC who had failed previous chemotherapy (17,20,28,29). In a study of 36 Taiwanese patients with pre-treated NSCLC, three patients had a complete response and nine had a partial response, with an overall response rate of 33.3% (17). Median survival was 9.5 months and the 1-year survival rate was 45.1%. A Chinese multicenter trial reported that in 159 patients treated with gefitinib, the objective response rate was 27% and the disease control rate was 54% (20). The 1-year survival rate was 44% and the median overall survival was 10 months.

The Phase II SIGN (second-line Indication of Gefitinib in NSCLC) study was an open-label, randomized study in 141 patients with pre-treated advanced NSCLC of single-agent gefitinib (250 mg/day) or docetaxel (75 mg/m^2 every 3 weeks) conducted in Europe, South America and the Middle East (18). Efficacy of gefitinib was found to be similar to docetaxel with regard to symptom improvement rates (36.8 versus 26%), quality of life improvement rates (33.8 versus 26%), objective response rates (13.2 versus 13.7%) and overall survival (7.5 versus 7.1 months).

Phase III Studies

ISEL (Iressa Survival Evaluation in Lung Cancer) was a double-blind, placebo-controlled, parallel-group, multicenter, randomized, Phase III study to assess the survival advantage of gefitinib (250 mg/day) as second- or third-line treatment for patients with locally advanced or metastatic NSCLC (25). A total of 1692 patients were recruited from 210 centers in 28 countries across Europe, Asia, Central and South America, Australia and Canada who were either refractory to or intolerant of their last chemotherapy regimen. Approximately 20% of patients in each treatment group were of Asian origin. There was some improvement in survival with gefitinib, compared with placebo, in the overall population, with median survivals of 5.6 and 5.1 months, respectively, but this failed to reach statistical significance [hazard ratio (HR) 0.89; 95% confidence interval (CI) 0.77–1.02; $P = 0.087$]. The large number of chemotherapy-refractory patients (90%) in this study is the most likely explanation for the outcome as these patients represent a very difficult-to-treat population with poor prognosis. In the overall population, gefitinib significantly improved objective response rate [8% versus 1.3%, odds ratio 7.28 (95% CI 3.1–16.9), $P < 0.0001$] and time to treatment failure [3 versus 2.6 months, odds ratio 0.82 (95% CI 0.73–0.92), $P = 0.0006$], compared with placebo.

Pre-planned sub-group analyses showed a significant overall survival benefit for gefitinib versus placebo in never smokers (median 8.9 versus 6.1 months; HR 0.67; 95% CI 0.49–0.92; $P = 0.012$) and in patients of Asian origin (9.5 versus 5.5 months; HR 0.66; 95% CI 0.48–0.91; $P = 0.01$) when compared with placebo (27). Sub-group analyses also showed a higher objective response rate for gefitinib than for placebo in all sub-groups, with the largest differences among never smokers, women, patients with adenocarcinoma histology and patients of Asian origin. These results are consistent with the subset analyses performed on response data from the Phase II IDEAL studies (19,22).

Exploratory biomarker analyses showed a trend towards a better survival outcome on gefitinib, compared with placebo, in patients with high EGFR-gene-copy number [assessed by fluorescent in situ hybridization (FISH)] (31). In patients with a high EGFR-gene-copy number (114 patients, 30.8%), the risk of death during the follow-up period was 39% lower among patients receiving gefitinib compared with those receiving placebo (HR 0.61; 95% CI 0.36–1.04; $P = 0.067$). No apparent difference in survival between gefitinib and placebo was observed in patients with a low EGFR-gene-copy number (HR 1.16; 95% CI 0.81–1.64; $P = 0.417$). The statistically significant treatment by EGFR-gene-copy number interaction test ($P = 0.045$) indicated that the HRs for patients with high EGFR-gene-copy number (0.61) and low EGFR-gene-copy number (1.16) were different (i.e. that EGFR-gene-copy number was a predictor of survival benefit with gefitinib compared with placebo). Survival hazard ratios in favor of gefitinib-treated patients who had a high EGFR-gene-copy number were observed even in patients with clinical factors usually considered to be least likely to benefit [smokers (HR 0.68; 95% CI 0.39–1.17; $P = 0.162$) and patients with non-adenocarcinoma histology (HR 0.61; 95% CI 0.31–1.22; $P = 0.163$)]. With gefitinib, longer median survival was seen in patients with a high versus low EGFR-gene-copy number (8.3 versus 4.3 months, respectively; HR 0.78; 95% CI 0.54–1.13). In contrast, with placebo, shorter median survival was seen in patients with a high versus low EGFR-gene-copy number (4.5 versus 6.2 months, respectively; HR 1.41; 95% CI 0.84–2.35),

indicating that the longer survival in gefitinib-treated patients with a high EGFR-gene-copy number was unlikely to be due to a prognostic effect. EGFR protein expression was also related to clinical outcome (HR 0.77; 95% CI 0.56–1.08; $P = 0.126$; interaction test $P = 0.049$). Furthermore, patients with high EGFR-gene-copy number and EGFR protein expression seemed to achieve better response rates with gefitinib (16.4 and 8.2%) than those without (3.2 and 1.5%, respectively). EGFR mutation data were available for 215 patients and a higher response rate with gefitinib was found among patients with EGFR mutations (37.5%) compared with those without (2.6%).

More recently, three Phase III studies have compared gefitinib versus docetaxel in pre-treated NSCLC. INTEREST (Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere), the largest prospectively randomized Phase III study comparing an EGFR-TKI to chemotherapy in pre-treated advanced NSCLC involved 1466 patients from 24 countries, 21% of whom were from Asia (21). INTEREST met its primary objective and demonstrated the non-inferiority of gefitinib relative to docetaxel in terms of overall survival in the total study population. The HR for gefitinib versus docetaxel was 1.02 and the 96% CI was 0.905–1.150, meeting the pre-defined non-inferiority criterion of 1.154. However, the hypothesis of superiority in overall survival for gefitinib relative to docetaxel in the 174 patients with high EGFR-gene-copy number was not proved (HR 1.09; 95% CI 0.78–1.51; $P = 0.620$). Interestingly, sub-group analyses showed that patients with characteristics that have been associated with an enhanced benefit on gefitinib in previous studies and clinical experience (i.e. Asian origin, never-smoker status, adenocarcinoma histology and female gender) had similarly long survival times on both gefitinib and docetaxel. In patients of Asian origin, median overall survival was 10.4 versus 12.2 months for gefitinib versus docetaxel (HR 1.04; 95% CI 0.80–1.35; $P = 0.7711$) and in patients of non-Asian origin, median overall survival was 6.9 months for both treatment arms (HR 1.01; 95% CI 0.89–1.14; $P = 0.9259$) (21).

V-15-32 was a smaller, Phase III, open-label study of gefitinib versus docetaxel in 490 pre-treated Japanese patients with locally advanced/metastatic NSCLC (24). The primary endpoint was overall survival and the study aimed to show non-inferiority of gefitinib versus docetaxel. Although the non-inferiority of survival for gefitinib compared with docetaxel was not statistically proved according to a pre-specified criteria of upper confidence interval <1.25 (HR 1.12; 95.24% CI 0.89–1.40), gefitinib survival was not statistically shorter than docetaxel ($P = 0.330$). A supportive adjusted analysis of overall survival, accounting for pre-defined factors, showed a HR of 1.01 (95% CI 0.80–1.27), fully compatible with the large INTEREST trial. This suggests that an imbalance in demography may be have impacted on the primary unadjusted overall survival result. The median survival and the 1-year survival rates were 11.5 months and 47.8%, respectively, for gefitinib and 14 months and 53.7%, respectively, for docetaxel. Imbalances in post-discontinuation treatment have complicated the interpretation of the survival data in this study. There was a subsequent high gefitinib prescription in the docetaxel arm in certain sub-groups (for example, approximately two-thirds of docetaxel never-smokers and females had gefitinib as their first post-study treatment); this may have been reflected in the increased survival in these sub-groups. Median progression-free survival was 2 months for both treatments (HR 0.90; 95% CI 0.72–1.12; $P = 0.335$). The overall response rate was statistically greater for gefitinib than docetaxel (22.5 versus 12.8%; odds ratio 2.14; 95% CI 1.21–3.78; $P = 0.009$) and was consistent with sub-group analyses of gefitinib-treated Japanese patients from the IDEAL 1 study. Gefitinib showed statistically significant benefits compared with docetaxel in quality of life improvement rates (FACT-L (Functional Assessment of Cancer Therapy-Lung): 23.4 versus 13.9%; $P = 0.023$; TOI (Trial Outcome Index): 20.5 versus 8.7%; $P = 0.002$), there were no significant differences between treatment arms in symptom improvement rates [LCS (Lung Cancer Subscale) 22.7 versus 20.4%; $P = 0.562$].

ISTANA (Iressa as Second Line Therapy in Advanced NSCLC-Asia) was a Phase III study that compared gefitinib and docetaxel in pre-treated advanced NSCLC in 161 Korean patients with advanced NSCLC (23). This study reported promising results that indicated that progression-free survival was significantly longer with gefitinib compared with docetaxel [HR 0.73; 90% CI 0.53–1; $P = 0.0441$ (one-sided P-value)]. Although ISTANA was a smaller Phase III study in which mature survival data are not yet available, this progression-free survival result in a Korean patient population supports the outcome of several other Phase II and III studies, including INTEREST, V-15-32 and SIGN (18,21,24). Early analysis of overall survival suggests that survival may be longer with gefitinib compared with docetaxel but the number of events is small and follow-up is ongoing (23). Objective response rate was higher with gefitinib compared with docetaxel (28.1 versus 7.6%, respectively; $P = 0.0007$); again, this is consistent with the results seen in V-15-32 (24).

GEFITINIB IN FIRST-LINE ADVANCED NSCLC

Gefitinib is not currently approved for first-line use but clinical evaluation of the drug in this setting is ongoing. A summary of studies of gefitinib in the first-line setting in patients with advanced NSCLC is included in Table 2 (32–51).

In Combination with Cytotoxics and in the Maintenance Setting

Two Phase III, randomized, double-blind and placebo-controlled trials investigated gefitinib (250 and 500 mg/day) in combination with standard first-line cytotoxics. In INTACT 1 (The Iressa NSCLC Trial Assessing Combination Treatment), conducted in 1093 patients in Europe, North

Table 2. Summary of gefitinib 250 mg/day efficacy data in Phase II and III studies in chemotherapy-naïve patients with advanced NSCLC[a]

Trial	Patient selection criteria	Phase	Patient origin	Number of selected patients receiving gefitinib 250 mg/day	Response rate (%)	TTP/PFS (months)	MST (months)	1-year survival (%)
Plus cytotoxics								
INTACT 1 (32)	Unselected	III	World	336	51.2	5.8	9.9	41
INTACT 2 (34)	Unselected	III	80% USA	232	30.4	5.3	9.8	41
WJTOG (35)	Unselected	III	Japan	300	34.2	4.6	11.4	—
As monotherapy								
Hashizume et al. (33)	Unselected	II	Japan	19	21	—	6.8	27
Lee et al. (36)	Clinically selected	II	Korea	72	55.6	6.8	19.7	—
Lin et al. (37)	Unselected	II	Taiwan	53	32.1	3.2	9.4	41.5
IPASS (38)	Clinically selected	III	Asia	1217	43	—	18.6	—
Niho et al. (39)	Unselected	II	Japan	42	30	—	13.9	55
Reck et al. (40)	Unselected	II	Germany	58	5.2	1.8	7.3	—
Suzuki et al. (41)	Unselected	II	Japan	34	26.5	—	14.1	58.2
Yang et al. (42)	Unselected	II	Taiwan	106	50.9	5.5	22.4	—
Exon 19 deletion	EGFR mutation			20	95	8.9	—	—
Exon 21 mutation				23	73.9	9.1		
Kimura et al. (43)	Unselected	II	Japan	28	—	3.2	10.2	—
	EGFR mutation			13	77.8	6.7	20.4	—
Spigel et al. (44)	Unselected	II	United States	70	4	3.7	6.3	24
Agiris and Mittal (45)	Unselected	II	United States	25	18	2.2	12.6	52
D'Addario et al. (46)	Unselected	II	Switzerland	63	8	2.5	11.5	—
Asahina et al. (47)	EGFR mutation	II	Japan	16	75	8.9	—	—
Inoue et al. (48)	EGFR mutation	II	Japan	16	75	9.7	—	—
Tamura et al. (49)	EGFR mutation	II	Japan	28	75	11.5	NR	79
iTARGET mutation (50)	EGFR mutation	II	United States					
Exon 19 deletion				18	59	9.2	17.5	73
Exon 21 mutation				9	78	9.2	17.5	73
I-CAMP (51)	EGFR mutation	II	Japan	148	76.4	9.7	24.3	—

[a]Studies shown are Phase II and III studies identified for this review article from the database searches conducted; EGFR, epidermal growth factor receptor; NR, not reached; INTACT, The Iressa NSCLC Trial Assessing Combination Treatment; WJTOG, West Japan Thoracic Oncology Group; IPASS, Iressa Pan ASian Study.

America, South America, South Africa and Asia, gefitinib was combined with gemcitabine and cisplatin. In INTACT 2, in 1037 chemotherapy-naïve patients with advanced NSCLC, 80% from the USA, gefitinib was combined with paclitaxel and carboplatin. Neither dose of gefitinib increased overall survival in combination with the cytotoxics (32,34). However, both trials did confirm, in a placebo-controlled setting, the favorable gefitinib safety profile observed in other trials.

The Phase III West Japan Thoracic Oncology Group maintenance trial (WJTOG) investigated gefitinib maintenance therapy after platinum-doublet chemotherapy in over 600 Japanese patients with advanced NSCLC (35). Patients were randomized to either platinum doublet-chemotherapy (carboplatin plus paclitaxel, cisplatin plus irinotecan, cisplatin plus vinorelbine, cisplatin plus docetaxel or cisplatin plus gemcitabine) for up to six cycles or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg/day. Gefitinib patients had a statistically significant improvement in progression-free survival compared with those remaining on chemotherapy (HR 0.68; 95% CI 0.57–0.80; $P < 0.001$); however, the primary endpoint of overall survival result did not reach statistical significance (HR 0.86; 95% CI 0.72–1.03; $P = 0.10$). In a pre-specified analysis of overall survival by histologic groups, gefitinib patients with adenocarcinoma histology had significantly better overall survival (HR 0.79; 95% CI 0.65–0.98; $P = 0.03$).

As First-Line Monotherapy

Several Phase II studies have investigated gefitinib as first-line monotherapy in patients with advanced NSCLC. In patients of Asian origin, response rates of ~30% have been reported (33,36–39,41,42), which are considerably higher than those reported in first-line studies of patients of non-Asian origin (<10%) (40,44–46) (Table 2). For example, Niho et al.'s (39) study of 42 Japanese chemotherapy-naïve NSCLC patients reported a response rate of 30%, median survival time of 13.9 months and a 1-year survival rate of 55%. A single-arm study was performed by Suzuki et al. (41) which evaluated the efficacy and tolerability of gefitinib in 34 Japanese patients with previously untreated NSCLC. Objective tumor response rate was 26.5%. Lin et al.'s (37) single arm study of 53 Taiwanese NSCLC patients reported an objective response rate of 32.1% and an overall disease control rate of 52.8%. Progression-free survival was 3.2 months. In comparison, Reck et al.'s (40) Phase II study in Germany of 58 chemotherapy-naïve patients with inoperable NSCLC receiving gefitinib 250 mg/day first-line reported an overall response rate of 5%, median progression-free survival of 1.8 months and median overall survival of 7.3 months. Spigel et al.'s (44) US Phase II study of 70 chemotherapy-naïve patients with poor performance status and advanced NSCLC receiving gefitinib 250 mg/day first-line reported a median progression-free survival and overall survival of 3.7 and 6.3 months, respectively.

IPASS (Iressa Pan Asian Study), a Phase III, open-label, randomized study compared gefitinib versus carboplatin and paclitaxel as first-line treatment in clinically selected patients with advanced NSCLC in Asia. The IPASS hypothesis was based on the identification of clinical characteristics that predicted response to gefitinib relative to placebo in the ISEL study plus the evidence from non-comparative single-arm studies in the first-line setting. This recently reported study exceeded its primary objective (to assess for non-inferiority of progression-free survival) and demonstrated superiority of gefitinib relative to carboplatin/paclitaxel doublet-chemotherapy in terms of progression-free survival (HR 0.74; 95% CI 0.65–0.85; $P < 0.0001$) (38). The HR was not constant over time, favoring carboplatin/paclitaxel for the first 6 months and then gefitinib for the remaining 16 months, potentially driven by differences in outcomes in patients with EGFR mutation-positive and negative tumors.

TOLERABILITY

Gefitinib is generally well tolerated with the most common AEs being low-grade, mild-to-moderate skin rash and diarrhea (21,25,52). Other AEs observed with the use of gefitinib include dry skin, pruritus, acne, nausea, vomiting, anorexia, asthenia and asymptomatic elevations in liver transamine levels. Tolerability data from the ISEL and INTEREST studies are shown in Table 3 (21,25). In the ISEL study, most patients experienced at least one AE (82% in the gefitinib group and 71% in the placebo group) (25). The most common AEs in the gefitinib group were rash and diarrhea. The overall frequency of Grade 3 or 4 AEs was 30% for gefitinib versus 27% for placebo, and AEs leading to withdrawal were experienced in 5 and 2%, respectively.

Well-recognized AEs associated with cytotoxic chemotherapy (such as bone marrow depression, neurotoxicity and nephrotoxicity) are not typically observed with gefitinib, as illustrated by the INTEREST and V-15-32 studies (21,24). INTEREST demonstrated a more favorable toxicity profile and significantly higher clinical improvement in quality of life for gefitinib when compared with chemotherapy (21). Gefitinib patients had fewer serious AEs (22.1 versus 29.4%), fewer AEs leading to discontinuation of treatment (8.1 versus 14.3%) and fewer treatment-related Grade 3 or 4 AEs (8.5 versus 40.7%) than docetaxel patients. Reports of skin rash and diarrhea were higher in gefitinib-treated patients than chemotherapy-treated patients, and cases of AEs typically associated with chemotherapy, including neurotoxicity and asthenia, were lower with gefitinib (Table 3). Similar results were reported in the V-15-32 study, where the gefitinib toxicity profile was consistent with its prescribing information and other reported studies in this setting (24). Gefitinib was associated with fewer dose interruptions and delays than docetaxel (26 versus 52%, respectively) and fewer Grade 3 to 4 AEs occurred with gefitinib compared with docetaxel (40.6 versus 81.6%, respectively) (24).

The IDEAL studies have reported the frequency and severity of gefitinib-related AEs to be dose-related, to generally occur during the first month of treatment, to be manageable, and non-cumulative (19,22,53). Interestingly, although AEs to gefitinib were known to be dose-related, as discussed earlier, the 500 mg dose did not show greater efficacy than the 250 mg dose. On the basis of the IDEAL studies, the optimal biological dose for gefitinib (250 mg/day) was defined and taken into Phase III studies.

Data from the ISEL and IDEAL 1 studies (19,25) have shown that the AE profile for gefitinib in Asian and non-Asian patients is similar although the ISEL study reported more patients of Asian origin experiencing at least one AE with both gefitinib and placebo (97 versus 82% for gefitinib; 87 versus 71% for placebo) and the frequency of Grade 3 or 4 AEs was also slightly higher (43 versus 30% for gefitinib; 36 versus 27% for placebo) (25).

ILD in Japanese NSCLC Patients

ILD has been reported in Japanese NSCLC patients receiving gefitinib at higher rates than outside Japan (15,54–57). ILD, especially idiopathic pulmonary fibrosis, is a known co-morbidity in patients with NSCLC and has been associated with many lung cancer therapies. When associated with drug use, it can present precipitously with acute alveolar damage, which can be fatal in some patients (58). Rates of acute ILD events up to and including 10% and have been reported in patients receiving chemotherapy and radiotherapy (56,59).

Table 3. Summary of adverse events occurring with gefitinib 250 mg/day therapy in the INTEREST (over 10% frequency) and ISEL (over 5% frequency) studies

INTEREST Study (21)					ISEL Study (25)			
Adverse event	Gefitinib All AEs ($n = 729$)	Docetaxel All AEs ($n = 715$)	Gefitinib CTC Grade 3/4 AEs ($n = 729$)	Docetaxel CTC Grade 3/4 AEs ($n = 715$)	Gefitinib All AEs ($n = 1126$)	Placebo All AEs ($n = 562$)	Gefitinib CTC Grade 3/4 AEs	Placebo CTC Grade 3/4 AEs
Neutropenia[a]	35 (5.0)[b]	514 (73.7)[b]	15 (2.2)[c]	406 (58.2)[c]	—	—	—	—
Febrile Neutropenia	9 (1.2)	72 (10.1)	9 (1.2)	72 (10.1)	—	—	—	—
Rash/acne[d]	360 (49.4)	73 (10.2)	15 (2.1)	4 (0.6)	413 (37.0)	56 (10.0)	18 (2.0)	1
Asthenic conditions[d]	182 (25.0)	334 (46.7)	32 (4.4)	64 (9.0)	141 (13.0)	71 (13.0)	36 (3.0)	15 (3.0)
Diarrhea	255 (35.0)	177 (24.8)	18 (2.5)	22 (3.1)	309 (27.0)	52 (9.0)	31 (3.0)	5 (1.0)
Nausea	148 (20.3)	187 (26.2)	3 (0.4)	9 (1.3)	190 (17.0)	90 (16.0)	9 (1.0)	2
Anorexia[d]	159 (21.8)	151 (21.1)	11 (1.5)	7 (1.0)	193 (17.0)	77 (14.0)	26 (2.0)	11 (2.0)
Alopecia	23 (3.2)	254 (35.5)	—	—	—	—	—	—
Dyspnea	120 (16.5)	117 (16.4)	45 (6.2)	55 (7.7)	75 (7.0)	44 (8.0)	35 (3.0)	21 (4.0)
Vomiting	109 (15.0)	123 (17.2)	4 (0.5)	8 (1.1)	152 (14.0)	56 (10.0)	13 (1.0)	2
Neurotoxicity[d]	49 (6.7)	171 (23.9)	1 (0.1)	17 (2.4)	—	—	—	—
Cough	108 (14.8)	102 (14.3)	6 (0.8)	5 (0.7)	75 (7.0)	45 (8.0)	2	4
Constipation	79 (10.8)	121 (16.9)	6 (0.8)	13 (1.8)	108 (10.0)	71 (13.0)	13 (1.0)	10 (2.0)
Pyrexia	69 (9.5)	118 (16.5)	2 (0.3)	4 (0.6)	79 (7.0)	27 (5.0)	7	2
Fluid retention[d]	48 (6.6)	112 (15.7)	0	5 (0.7)	—	—	—	—
Stomatitis[d]	67 (9.2)	93 (13.0)	0	3 (0.4)	68 (6.0)	22 (4.0)	3	1
Lower RTI and lung infections[d]	71 (9.7)	74 (10.3)	23 (3.2)	25 (3.5)	—	—	—	—
Myalgia	24 (3.3)	113 (15.8)	1 (0.1)	4 (0.6)	—	—	—	—
Dry skin	111 (15.2)	10 (1.4)	0	0	128 (11.0)	20 (4%)	0	0
Anemia	34 (4.7)	84 (11.7)	11 (1.5)	15 (2.1)	—	—	—	—
Pruritus[d]	—	—	—	—	93 (8.0)	27 (5.0)	4	1
Hemoptysis	—	—	—	—	59 (5.0)	24 (4.0)	5	2
Pneumonia	—	—	—	—	48 (4.0)	30 (5.0)	30 (3.0)	15 (3.0)
Cancer pain	—	—	—	—	39 (4.0)	36 (6.0)	7	3
Edema peripheral	—	—	—	—	39 (4.0)	33 (6.0)	1	5 (1.0)
Paronychia	—	—	—	—	35 (3.0)	0	1	0

RTI, respiratory tract infection; CTC, common toxicity criteria; AE, adverse event; ISEL, Iressa Survival Evaluation in Lung Cancer; INTEREST, Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere. Data are numbers (%) of patients. [a]Data from lab reports. Calculations include only patients with a baseline and at least one postbaseline value. [b]Worsening in lab value from baseline. [c]Worsening in lab value from baseline to CTC grade 3/4. $n = 697$ for neutropenia with gefitinib and docetaxel. [d]Grouped term (sum of preferred terms).

Post-marketing surveillance (by AstraZeneca) of 3322 Japanese patients treated with gefitinib found that the reporting rate of ILD-type incidences was 5.8% (60), consistent with the rate of ILD observed in the Japanese V-15-32 study (5.7 versus 2.9% for docetaxel) (24). The INTEREST study, with a predominantly western population, reported ILD-type events for 1.4% patients receiving gefitinib versus 1.1% patients receiving docetaxel, highlighting the lower ILD incidence in the rest of the world when compared with Japan (21). INTEREST is also consistent with the worldwide ISEL study, which reported a similar frequency of ILD events for patients receiving gefitinib and placebo treatment groups of patients (1% for both groups) (25). Reported rates for ILD in studies conducted in other East Asian countries are lower than in studies in Japan, including the ISTANA study, where an ILD rate of 3.7% was reported in Korean patients receiving gefitinib versus 3.9% for docetaxel (23). Yang et al.'s (42) study of Taiwanese NSCLC patients receiving gefitinib first-line reported ILD-type events occurring in 0.9% of patients.

The gefitinib case–control study (CCS) was a pharmacoepidemiologic study designed and conducted by an academic team in collaboration with AstraZeneca (54). This pivotal study reported, for the first time, the risk of acute ILD events for a large and unselected chemotherapy-treated NSCLC

patient cohort in Japan and quantified the greater risk of developing acute ILD associated with gefitinib treatment than with chemotherapy. The observed incidence rate over 12 weeks was, per 1000 person-weeks, 4.5 for gefitinib and 1.7 for chemotherapy; the corresponding observed, naïve, cumulative incidence rates at the end of 12-week follow-up were 4.0 and 2.1%, respectively. The mortality due to ILD for the patients who developed acute ILD was 31.6% among gefitinib-treated patients and 27.9% among those receiving other treatments. The study also reported that risk factors, regardless of treatment, included older age, poor performance status, smoking history, recent NSCLC diagnosis, reduced normal lung on CT scan, pre-existing chronic ILD and concurrent cardiac disease.

Dosing Strategies for Gefitinib

Based on the results of the IDEAL studies, gefitinib is dosed at its optimal biological dose of 250 mg/day, and is given in the form of a once-daily tablet. This is above the lowest dose at which clinical responses are seen and is significantly lower than the reported maximum tolerated dose (MTD, 700 mg/day). Gefitinib 250 mg/day is well tolerated, ensures adequate gefitinib exposure and has been shown to inhibit EGFR signaling in skin biopsies. (14,61,62). Phase III studies have shown that gefitinib 250 mg/day is equivalent to docetaxel for overall survival (21) and in Asian patients gefitinib 250 mg/day is significantly better than placebo (25). Gefitinib is ~60% absorbed after oral administration and once absorbed is 90% protein-bound. Peak plasma concentrations are reached within 3–7 h after dosing and the mean terminal half-life has been shown to be 41 h in cancer patients. Excretion is predominantly through the feces (86%), with renal elimination of drug and metabolites accounting for >4% of the administered dose. Steady-state concentrations are usually achieved within 7–10 days of daily dosing in cancer patients. The large volume of distribution in cancer patients (1400 l) indicates extensive distribution into tissues, including tumor tissue (14,63,64). Haura et al.'s (65) recently reported pilot Phase II study of preoperative gefitinib in early stage NSCLC assessed intratumor gefitinib levels and reported a mean concentration of 33 100 $\pm$ 44 300 versus 531 $\pm$ 344 nM in plasma, following 28 days' treatment with gefitinib. Gefitinib's pharmacokinetic properties result in a significant drug accumulation in the tumor tissue which allows the use of its optimal biological dose rather than the traditional MTD. The optimal biological dose of 250 mg/day provides a better benefit/risk profile for gefitinib as it is associated with less toxicity but not with lower efficacy, than the higher 500 mg/day dose.

EGFR MUTATIONS AND PATIENT RESPONSE TO GEFITINIB

Considerable effort has gone into researching the apparent differences in rate of objective response between Asian and non-Asian patient to EGFR-TKIs and understanding any evidence that may suggest an underlying biological basis. Several studies (in both chemotherapy-naïve NSCLC patients and those with previously treated NSCLC) have shown that patients who are particularly responsive to gefitinib have tumors containing somatic activating mutations in the EGFR gene. A response rate of ~75% has been reported in EGFR mutation-positive patients of Asian origin receiving gefitinib first-line (47–49). Response rates of ~50% have been reported in non-Asian patients who are EGFR mutation-positive (50). Response rates in EGFR mutation-positive patients receiving gefitinib after previous chemotherapy have been reported to be between 76 and 91% in Asian studies (66,67) and between 58 and 70% in non-Asian patients (68,69). The most common mutations reported occur in exons 18–21 and are small, in-frame deletions or amino acid substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain (42,55,70–73). At least two of the common mutation types (deletions in exon 19 and the L858R missense mutation) are associated with an increase in the amount and duration of ligand-dependent activation, which explains the much greater sensitivity to EGFR-TKIs of cells bearing these mutations (72). Greater sensitivity of mutation-positive cells to EGFR-TKIs results in greater inhibition of the intracellular tyrosine kinase domain of the EGFR and blocking of the signal transduction pathways implicated in the proliferation and survival of cancer cells. The cells with EGFR mutations become 'oncogene addicted' and respond to EGFR-TKI therapy with a significant increase in apoptosis, which translates to the tumor shrinkage reported in clinic.

Response to Gefitinib in Chemotherapy-Naïve NSCLC Patients with EGFR Mutations

Data available from studies of chemotherapy-naïve NSCLC patients receiving gefitinib as first-line therapy suggest that benefit from gefitinib in this patient group may be confined to EGFR mutation-positive patients (Table 2) (42,43,47–51). Yang et al.'s (42) study of 106 Taiwanese chemotherapy-naïve NSCLC patients receiving gefitinib as first-line monotherapy reported that patients with adenocarcinoma histology and EGFR exon 19 deletion or L858R mutations (analyzed by direct forward and reverse sequencing) had longer time to treatment failure (TTF) than patients without mutations (median TTF, 5.5 months; exon 19 deletion, 8.9 months; L858R mutation, 9.1 months). Sequist et al. (50) recently reported the multicenter iTARGET study that examined first-line gefitinib in advanced NSCLC patients in the USA. Ninety-eight patients with at least one clinical characteristic associated with EGFR mutation were screened and the 34 (35%) found to be harboring mutations were treated with gefitinib (50). iTARGET explored the significance of EGFR mutation subtypes and TKI resistance mechanisms. The most common EGFR mutations identified by Mutation Surveyor sequence analysis software were in-frame exon 19

deletions and L858R point mutation, comprising 53 and 26% of the mutation-positive cases, respectively. Although the study included clinical sub-groups known to be responders to EGFR-TKI (females, never-smokers, adenocarcinoma histology, Asian ethnicity), never-smoking was the only characteristic that predicted EGFR mutation status ($P = 0.02$). The study reported a significant clinical benefit for EGFR mutation-positive patients with an overall response rate of 55%, median progression-free survival of 9.2 months and median overall survival of 17.5 months, approximately 2-fold greater than typical chemotherapy regimens in unselected NSCLC populations. No statistical difference was reported in overall response rate among the two mutation groups (78 and 59% for exon 21 and 19, respectively).

Other studies have looked at EGFR mutation-positive patients in Asia receiving EGFR-TKI first-line (43,47–49). Asahina reported an overall response rate of 75% and disease control rate (complete response+partial response+stable disease) of 81% in a Phase II study of 16 mutation-positive Japanese patients receiving gefitinib first-line for advanced NSCLC (47). Three patients had an L858R point mutation in exon 21 and 13 patients had deletions in or near E746-A750 in exon 19, analyzed by Basic Local Alignment Search Tool (BLAST). Although the number of L858R patients was small, no significant difference was evident between type of mutation and response rate (exon 19 deletions, 83 versus L858R, 67%; $P = 0.87$). Tamura et al. (49) reported an overall response rate of 75% and disease control rate of 96% in a Phase II study of 28 mutation-positive Japanese patients receiving gefitinib first-line. BLAST analysis found EGFR mutations at exon 19 (most commonly deletions at E746-A750) and at exon 21 (most commonly L858R point mutations). A Phase II Japanese study reported by Kimura et al. (43) showed that 78% of NSCLC patients showing a partial response to first-line gefitinib treatment had EGFR mutations [exon 19 E746-A750 deletion, $n = 12$; exon 21 L858R point mutation, $n = 1$; analyzed by Amplified Refractory Mutation System (ARMS) and Scorpion] and mutation-positive patients showed a longer median survival compared with mutation-negative patients (611 versus 232 days, respectively). Inoue et al. (48) reported an overall response rate of 75% and a disease control rate of 88% in 16 mutation-positive NSCLC patients (exon 19 E746-A750 deletion, $n = 9$; exon 21 L858R point mutation, $n = 7$; analyzed by BLAST) following treatment with gefitinib.

I-CAMP examined the efficacy and safety of gefitinib monotherapy for advanced NSCLC patients with EGFR mutations [most commonly exon 19 deletions or exon 21 L858R point mutations; analyzed by various methods including direct sequencing and Mutant Allele Specific Amplification (MASA)] and in a combined analysis of seven prospective Phase II trials conducted in Japan (51). Overall survival and progression-free survival data from the seven studies were updated and prognostic factors examined. A total of 148 patients were combined from the seven trials, with 57% of the patients receiving gefitinib as their first-line of therapy. It was found that median overall survival and progression-free survival were 24.3 months (95% CI 19.8–28.2) and 9.7 months (95% CI 8.2–11.1), respectively. Age ($P = 0.042$), histology ($P = 0.002$) and performance status ($P < 0.001$) were significantly related to longer progression-free survival. The combined response rate was 76% and only 6% of the patients had progressive disease, indicating that gefitinib produced significant anti-tumor activity and prolonged survival in this selected NSCLC population.

Response to Gefitinib in Pre-treated NSCLC Patients with EGFR Mutations

Higher response rates have been reported in Asian EGFR mutation-positive NSCLC patients when receiving gefitinib second-line (66,67,74). However, unlike NSCLC patients who receive gefitinib first-line, outcome from gefitinib therapy in patients who had previously received chemotherapy appears to be consistent across both EGFR mutation-positive and -negative sub-groups when compared with chemotherapy. Data from the INTEREST study showed that overall survival was equally longer with both gefitinib and docetaxel treatments in EGFR mutation-positive (exons 18–21 on chromosome 7; analyzed by ARMS) patients ($n = 44$; 14.2 and 16.6 months, respectively) than in EGFR-negative patients ($n = 253$; 6.4 and 6.0 months, respectively) (75). However, progression-free survival was longer ($n = 38$; HR 0.16, 95% CI 0.05–0.49; $P = 0.001$) and objective response rate higher (42 versus 21%; $P = 0.04$) with gefitinib than docetaxel in EGFR mutation-positive patients. Biomarker analysis in the Japanese V-15-32 study showed that EGFR mutation-positive patients (analyzed by direct sequencing of exons 18–21, mutation details not provided) appeared to have better progression-free survival than mutation-negative patients on both gefitinib and docetaxel treatments [gefitinib-positive versus gefitinib-negative HR 0.33; 95% CI 0.11–0.97 (17 events); docetaxel HR 0.15; 95% CI 0.04–0.57 (15 events)] (24).

Frequency of EGFR Mutations in Patient Sub-Groups

Sasaki et al.'s (70) investigation of the EGFR mutations and/or polymorphism status in 303 surgically treated Japanese NSCLC patients reported that EGFR kinase domain mutations were found in 75 of the patients. Eighty-six EGFR polymorphism cases (G2607A) were identified at exon 20 (analyzed by BLAST). G2607A polymorphism was significantly higher in non-adenocarcinoma tumors (37%) than in tumors with adenocarcinoma histology (25%, $P = 0.0415$) (70). Shigematsu et al.'s (76) study of 617 NSCLC tumors collected from patients undergoing surgical resection in Japan, Taiwan, USA and Australia detected a total of 134 EGFR TK domain mutations in 130 (21%, analyzed by PRISM direct sequencing) of the NSCLC samples. These mutations were found to be statistically significantly

more frequent in never-smokers than ever-smokers (51 versus 10%), in tumors with adenocarcinoma versus non-adenocarcimoma histology (40 versus 3%), in patients of East Asian origin versus other ethnicities (30 versus 8%), and in females versus males (42 versus 14%); $P < 0.001$ in all cases. Mutation status was not associated with patient age, clinical stage, the presence of bronchioalveolar histologic features or overall survival. The three most common mutations detected in the study were in exons 19, 20 and 21 and were in-frame deletions in exon 19 (11 types, E746-A750 being the most common), missense mutations in exon 21 (especially L858R) and in-frame duplications and/or insertions in exon 20 (eight types, most commonly ASV770-772 insertion). Paez et al. (77) reported that EGFR mutations (analyzed by direct sequencing) occur at a much higher rate in Japanese patients (26% of patients) than in those from the USA (2% of patients), indicating that differences in EGFR mutation rates may underlie differences in response rate to gefitinib between Asian and western populations. The highest proportion of EGFR mutations was observed in Japanese women with adenocarcinoma histology (57% of patients), which are findings supported by many more studies and reviews (70,71,78–84).

EGFR mutations have been found to be more common in adenocarcinoma than other histologies, in women than men, in never-smokers than smokers, and in patients receiving gefitinib first-line (42,77). Wu (78) surveyed the clinical data and mutational status of 328 NSCLC Taiwanese patients, who had received gefitinib and reported that 192 patients had mutant-EGFR, including 77 patients with exon 19 deletions and 75 patients with exon 21 point mutation L858R (analyzed by direct sequencing). Clinical response to gefitinib was the only factor associated with better overall survival ($P = 0.001$), indicating that gefitinib is effective in mutant-EGFR patients (78).

A study of East Asian women reported by Bell et al. (81) hypothesized that the appreciably higher prevalence of EGFR-mutant NSCLC in females than males and in East Asians than in Caucasians may be attributable to genetic modifiers. Nine polymorphisms were genotyped by BLAST in a series of 100 Japanese NSCLCs, selected for equal representation of EGFR wild-type, EGFR mutant and male and female cases. Out of the nine polymorphisms genotyped, only the estrogen-related polymorphism CYP1A1 showed a difference in allele frequency that approached significance, suggesting that the selected polymorphic variants in the estrogen biosynthesis and metabolism pathways are unlikely to be major genetic modifiers of the prevalence of EGFR-mutant NSCLC.

Previous studies have demonstrated a dinucleotide repeat polymorphism (CA) in intron 1 of EGFR, ranging from 14 to 21 repeats that has been suggested to regulate EGFR expression (84,85). EGFR gene transcription activity declines with increasing number of CA repeats; therefore overexpression of EGFR with longer alleles may influence clinical outcome and increase drug response. In one study, a longer allele with 21 repeats showed an 80% reduction of gene expression compared with a shorter allele with 16 repeats (analyzed by Genescan) (85). Liu et al. (84) evaluated the influence of ethnicity on an EGFR intron 1 polymorphism by genotyping individuals (direct sequencing) of Caucasian ($n = 183$), African-American ($n = 84$) and Asian ($n = 66$) ethnicity. The frequency of a longer allele with 21 repeats of the polymorphism was found to be significantly higher in Asian individuals (63% compared with 21% in Caucasians, $P < 0.001$); the shorter allele with 16 repeats of the polymorphism was found to have a significantly lower frequency of occurrence in Asians (17% compared with 43% in Caucasians, $P < 0.001$). Liu et al.'s results indicate that major ethnic differences in the allelic frequencies of the EGFR intron 1 polymorphism exist that may help to provide understanding of the molecular basis underlying ethnic differences in gefitinib response.

Relationship Between Resistance to Gefitinib and EGFR Mutations

Although impressive responses to gefitinib have been observed in patients with EGFR mutations, tumor progression can occur as resistance develops. Research into this acquired resistance has focused on determining the factors underlying it: namely, a secondary mutation in the EGFR gene, T790M, amplification of the MET proto-oncogene, exon 20 insertions and gene profile signatures (70,72,73,86–88).

Zucali et al. (89) evaluated several potential biomarkers of intrinsic EGFR-TKI resistance in NSCLC and reported that EGFR exon 19 deletion (direct sequencing) and pAKT expression (immunohistochemistry) were significantly associated with response ($P < 0.0001$) and longer time to progression ($P = 0.007$), respectively. Strong cMET membrane immunoreactivity was expressed in 6% of 149 tumors analyzed and was significantly associated with progressive disease ($P = 0.019$) and shorter time to progression ($P = 0.041$), indicating that cMET appears to be a marker of primary resistance in NSCLC patients.

Nishimura et al. (90) reported an *in vitro* study of gefitinib-resistant QG56 cells that postulated that impairment in some steps of EGF-EGFR trafficking within cells may confer gefitinib resistance. EGFR trafficking through the early endocytic pathway was impaired in QG56 cells; therefore, gefitinib appeared to suppress slightly the internalization of pEGFR, conferring gefitinib resistance in the cells.

Janne et al.'s (91) review centered on a secondary mutation in the EGFR gene – T790M – which is thought to cause steric hindrance and impair the binding of gefitinib. Identification of the sub-group of patients with NSCLC whose tumors harbor EGFR T790M was deemed of extreme importance as only a few copies of the T790M allele are required to confer resistance, which may obscure results of conventional sequencing methods. Wang et al. (92) recently reported a small study investigating KRAS and EGFR mutation frequencies (analyzed by direct sequencing) in 24

Chinese patients with NSCLC. EGFR mutations were found in 62.5% of patients, although no KRAS gene mutations were found. Although KRAS mutations reportedly behave as a resistance marker to gefitinib, it is possible that the mutation may occur at a very low frequency in Chinese NSCLC patients, regardless of pathology, smoking status, or gender.

DISCUSSION

There is now a wealth of experience and clinical data relating to the use of gefitinib in patients with advanced NSCLC, many of these highlighting the clinical benefit in patients of Asian origin (70,71,78–81).

Pre-planned sub-group analyses in several studies, including IDEAL 1 and ISEL, have consistently shown higher overall survival and response rates with gefitinib in patients of Asian origin when compared with the overall population in pre-treated advanced NSCLC patients not eligible for chemotherapy (19,25,26). However, Asian ethnicity does not appear to be an important selection factor in pre-treated patients who are eligible for further chemotherapy, as shown by the INTEREST study, which reported that although Asian patients had longer overall survival than the overall population, they did equally well when treated with gefitinib or docetaxel (21).

In chemotherapy-naïve patients, there is no role for gefitinib in combination with doublet chemotherapy (32,34). More recent data from the WJTOG study (35) indicate that maintenance therapy following chemotherapy with gefitinib may improve patient outcome, especially in patients with adenocarcinoma histology. Significantly, the IPASS study has shown that gefitinib monotherapy can demonstrate superiority relative to doublet chemotherapy in terms of progression-free survival in a population of clinically selected Asian patients with advanced NSCLC (38).

A study undertaken by Ho et al. (93) in Canada reported that the preferential response to gefitinib seen in the Asian population is preserved in a western setting when comparing ethnicity versus country of habitation. The pathology, radiology, laboratory investigations and clinical records of 61 patients (38% Asian) treated with gefitinib for advanced NSCLC were reviewed. On radiologic review, 14 patients had a partial response, 10 of whom were Asian, 10 female, eight non-smokers, eight were adenocarcinoma and four bronchoalveolar variant. Most of the responders were patients of Asian ethnicity who had emigrated to Canada from China, Taiwan or Hong Kong, indicating a preserved molecular basis of the improved response rate irrespective of the geographical location of the patient.

Treatment tolerability is a significant issue for cancer patients and the incidence and severity of AEs in Asian patients has been consistent throughout gefitinib studies. The more favorable tolerability profile of gefitinib compared with those associated with chemotherapy, such as docetaxel, is well reported (19,21,24,25). Although the main AEs associated with gefitinib are generally mild to moderate skin rash and diarrhea, the higher incidence of ILD in Japanese patients must be noted. Rates of ILD following gefitinib treatment have recently been reported at 5.7% in the Japanese V-15-32 study (24) and 1.4% in the global INTEREST study (21). Particular sub-groups of Japanese NSCLC patients are known to be at higher risk of developing ILD whilst on gefitinib therapy, namely those of male gender, a history of smoking, pre-existing ILD or poor performance status (15,54,56). Therefore, consideration of gender, smoking history and performance status should be taken into account when making individual treatment decisions to minimize ILD risk and improve further the benefit-risk profile of gefitinib.

Many publications have focused on the role of genetic mutations in the increased response witnessed in Asian compared with western populations. There are a wealth of data on the higher occurrence of somatic mutations of the EGFR gene in Asian patients that may predict the greater sensitivity of NSCLC to gefitinib (71,79,84). A definite benefit has been reported for mutation-positive patients receiving gefitinib first-line when compared with those who are mutation-negative (43,49,94–99). I-CAMP has shown that gefitinib can improve median survival to over 2 years in mutation-positive NSCLC patients (51). It is clear from these studies that chemotherapy-naïve Asian EGFR mutation-positive patients have good efficacy outcomes with gefitinib; therefore, measurement of EGFR mutation, particularly in the first-line setting, is undoubtedly meaningful when making individual patient choices. Two ongoing, prospective, Phase III trials in Japan comparing gefitinib versus doublet chemotherapy in chemotherapy-naïve mutation-positive patients are of great interest.

The practicalities of trying to determine the mutation status of patients by biomarker analyses can prove problematic, even in controlled clinical trials, as there are many practical issues to overcome. Biopsies may not be available for patients and mutation tests on available biopsies may prove inconclusive.

Although there is a clinical benefit reported for mutation-positive patients receiving gefitinib first-line, mutation status does not appear to influence survival in NSCLC patients receiving gefitinib second- or third-line compared with chemotherapy. Exploratory biomarker analysis in the INTEREST study showed that there was no difference in survival between gefitinib and docetaxel according to EGFR mutation status; however, there appeared to be improved progression-free survival and higher response rates on gefitinib than docetaxel in a small sub-group of 44 EGFR mutation-positive patients (21). However, the co-primary analysis in the INTEREST study produced the unexpected result that, among patients with high EGFR-gene-copy number, which had been reported to be associated with improved survival with gefitinib compared with placebo, survival was not longer with gefitinib than docetaxel.

The role of biomarkers in pre-treated patients has not yet been formally identified and validated in prospective,

randomized Phase III clinical trials. The biomarker data are much less robust in pre-treated patients than in chemotherapy-naïve patients because analyses are performed on archival biopsies. The natural progression of the disease as well as exposure to prior systemic treatments can alter the tumor biology by the time second- or third-line treatment is initiated. All analyses performed to assess association of biomarkers with efficacy outcome in pre-treated patients have this limitation.

Studies are currently ongoing to further define the role of gefitinib in the treatment of advanced NSCLC, in Asian patients and elsewhere. Worldwide there are currently 20 gefitinib trials actively recruiting NSCLC patients and 56 trials that are currently active or completed (ClinicalTrials.gov). Asian patients have been specifically targeted in six current Phase II, III and IV gefitinib trials, two of which are using gefitinib as a first-line treatment in chemotherapy-naïve patients.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Detterbeck FC, Rivera MP, Socinski MA. Diagnosis and treatment of lung cancer: an evidence-based guide for the practicing physician. Philadelphia, WB Saunders 2000, (eds.).
3. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995;19:183–232.
4. Rusch V, Baselga J, Cordon-Cardo C, Orazem J, Zaman M, Hoda S, et al. Differential expression of the epidermal growth factor receptor and its ligands in primary non-small cell lung cancers and adjacent benign lung. *Cancer Res* 1993;53:2379–85.
5. Fujino S, Enokibori T, Tezuka N. A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. *Eur J Cancer* 1996;32A:2070–4.
6. Pavelic K, Banjac Z, Pavelic J, Spaventi S. Evidence for a role of EGF receptor in the progression of human lung carcinoma. *Anticancer Res* 1993;13:1133–8.
7. Volm M, Rittgen W, Drings P. Prognostic value of ERBB-1, VEGF, cyclin A, FOS, JUN and MYC in patients with squamous cell lung carcinomas. *Br J Cancer* 1998;77:663–9.
8. Jeon YK, Sung SW, Chung JH, Park WS, Seo JW, Kim CW, et al. Clinicopathologic features and prognostic implications of epidermal growth factor receptor (EGFR) gene copy number and protein expression in non-small cell lung cancer. *Lung Cancer* 2006;54: 387–98.
9. Adiseshaiah P, Vaz M, Machireddy N, Kalvakolanu DV, Reddy SP. A Fra-1-dependent, matrix metalloproteinase driven EGFR activation promotes human lung epithelial cell motility and invasion. *J Cell Physiol* 2008;216:405–12.
10. Yatabe Y, Takahashi T, Mitsudomi T. Epidermal growth factor receptor gene amplification is acquired in association with tumor progression of EGFR-mutated lung cancer. *Cancer Res* 2008;68:2106–11.
11. Okuda K, Sasaki H, Kawano O, Yukiue H, Yokoyama T, Yano M, et al. Epidermal growth factor receptor gene mutation, amplification and protein expression in malignant pleural mesothelioma. *J Cancer Res Clin Oncol* 2008;134:1105–11.
12. Tsakiridis T, Cutz JC, Singh G, Hirte H, Okawara G, Corbett T, et al. Association of phosphorylated epidermal growth factor receptor with survival in patients with locally advanced non-small cell lung cancer treated with radiotherapy. *J Thorac Oncol* 2008;3:716–22.
13. Negoro S, Nakagawa K, Fukuoka M, Kudoh S, Tamura T, Yoshimura N, et al. Final results of a phase I intermittent dose-escalation trial of ZD1839 ('Iressa') in Japanese patients with various solid tumours. *Proc Am Soc Clin Oncol* 2001;20:324 (Abstract 1292).
14. Ranson M, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J Clin Oncol* 2002;20:2240–50.
15. Park K, Goto K. A review of the benefit-risk profile of gefitinib in Asian patients with advanced non-small-cell lung cancer. *Curr Med Res Opin* 2006;22:561–73.
16. Armour A. Gefitinib in advanced non-small cell lung cancer: clinical experience in patients of Asian origin. *Asia Pac J Clin Oncol* 2007;3:66–78.
17. Chen YM, Perng RP, Tsai CM. Gefitinib treatment is highly effective in non-small-cell lung cancer patients failing previous chemotherapy in Taiwan: a prospective phase II study. *J Chemother* 2005;17:679–84.
18. Cufer T, Vrdoljak E, Gaafar R, Erensoy I, Pemberton K. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. *Anticancer Drugs* 2006;17:401–9.
19. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard J-Y, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21:2237–46.
20. Guan ZZ, Zhang L, Li L-Y, Jiang G-L, Liu X, Chu D, et al. Efficacy of gefitinib on Chinese patients with locally advanced or metastatic non-small-cell lung cancer: a clinical trial. *Ai Zheng* 2005;24:980–4.
21. Kim ES, Hirsch V, Mok T, Socinski M, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer: a randomised phase III trial (INTEREST). *Lancet* 2008;372:1809–18.
22. Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, 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. *J Am Med Assoc* 2003;290:2149–58.
23. Lee D, Kim S, Park K, Kim J, Lee J, Shin S, et al. A randomized open-label study of gefitinib versus docetaxel in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy. *J Clin Oncol* 2008;26(Suppl.) (Abstract 8025).
24. Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K, et al. Phase III study, V-15–32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008;26:4244–52.
25. Thatcher N, Chang A, Parikh P, Rodrigues PJ, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527–37.
26. Nishiwaki Y, Yano S, Tamura T, Nakagawa K, Kudoh S, Horai T, et al. Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study on gefitinib. *Gan To Kagaku Ryoho* 2004;31:567–73.
27. Chang A, Parikh P, Thongprasert S, Tan E-H, Perng R-P, Ganzon D, et al. Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006;1:847–55.
28. Chiu C-H, Tsai C-M, Chen Y-M, Chiang S-C, Liou J-L, Perng R-P. Gefitinib is active in patients with brain metastases from non-small cell

lung cancer and response is related to skin toxicity. *Lung Cancer* 2005;47:129–38.
29. Wang MZ, Li LY, Wang SL, Zhang XT, Zhong W, Zhang L. Efficacy and safety of gefitinib as monotherapy for Chinese patients with advanced non-small cell lung cancer. *Chin Med J (Engl)* 2006;119: 63–8.
30. Herbst RS, Maddox AM, Rothenberg ML, Small EJ, Rubin EH, Baselga J, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol* 2002;20:3815–25.
31. Hirsch FR, Varella-Garcia M, Bunn PA Jr, Franklin WA, Dziadziuszko R, Thatcher N, et al. Molecular predictors of outcome with gefitinib in a Phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006;24:5034–42.
32. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. *J Clin Oncol* 2004;22:777–84.
33. Hashizume T, Ogura T, Kozawa S, Kobayashi N, Tagawa A, Miyazawa N, et al. Gefitinib as a first-line therapy in patients with advanced non-small cell lung cancer. *Gan To Kagaku Ryoho* 2006;33:467–70.
34. Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol* 2004;22:785–94.
35. Hida T, Okamoto I, Kashii T, Satouchi M, Ichinose Y, Katakami N, et al. Randomised phase III study of platinum-doublet chemotherapy followed by gefitinib versus continued platinum-doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results of West Japan Thoracic Oncology Group trial (WJTOG). *J Clin Oncol* 2008;26 (Abstract LBA8012).
36. Lee DH, Han JY, Yu SY, Kim HY, Nam BH, Hong EK, et al. The role of gefitinib treatment for Korean never-smokers with advanced or metastatic adenocarcinoma of the lung: a prospective study. *J Thorac Oncol* 2006;1:965–71.
37. Lin W-C, Chiu C-H, Liou J-L, Chen Y-M, Perng R-P, Tsai C-M. Gefitinib as front-line treatment in Chinese patients with advanced non-small-cell lung cancer. *Lung Cancer* 2006;54:193–9.
38. Mok T, Wu YL, Thongprasert S, Yang C-H, Chu D, Saijo N, et al. Phase III, randomised, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer. *Ann Oncol* 2008;19(Suppl. 8) (viii1, Abstract LBA2).
39. Niho S, Kubota K, Goto K, Yoh K, Ohmatsu H, Kakinuma R, 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: 64–9.
40. Reck M, Buchholz E, Romer KS, Krutzfeldt K, Gatzemeier U, Manegold C. Gefitinib monotherapy in chemotherapy-naive patients with inoperable stage III/IV non-small-cell lung cancer. *Clin Lung Cancer* 2006;7:406–11.
41. Suzuki R, Hasegawa Y, Baba K, Saka H, Saito H, Taniguchi H, et al. A phase II study of single-agent gefitinib as first-line therapy in patients with stage IV non-small-cell lung cancer. *Br J Cancer* 2006;94: 1599–603.
42. Yang CH, Yu CJ, Shih JY, Chang YC, Hu FC, Tsai MC, et al. Specific EGFR mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. *J Clin Oncol* 2008;26:2745–53.
43. Kimura H, Kasahara K, Kawaishi M, Kunitoh H, Tamura T, Holloway B, et al. Detection of epidermal growth factor receptor mutations in serum as a predictor of the response to gefitinib in patients with non-small-cell lung cancer. *Clin Cancer Res* 2006;12:3915–21.
44. Spigel DR, Hainsworth JD, Burkett ER, Burris HA, Yardley DA, Thomas M, et al. Single-agent gefitinib in patients with untreated advanced non-small-cell lung cancer and poor performance status: a Minnie Pearl Cancer Research Network Phase II Trial. *Clin Lung Cancer* 2005;7:127–32.
45. Agiris A, Mittal N. Gefitinib as first-line, compassionate use therapy in patients with advanced non-small-cell lung cancer. *Lung Cancer* 2004;43:317–22.
46. D'Addario G, Rauch D, Stupp R, Pless M, Stahel R, Mach N, et al. Multicentre phase II trial of gefitinib first-line therapy followed by chemotherapy in advanced non-small-cell lung cancer (NSCLC): SAKK protocol 19/03. *Ann Oncol* 2008;19:739–45.
47. Asahina H, Yamazaki K, Kinoshita I, Sukoh N, Harada M, Yokouchi H, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small-cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer* 2006;95:998–1004.
48. Inoue A, Suzuki T, Fukuhara T, Maemondo M, Kimura Y, Morikawa N, 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;24:3340–6.
49. Tamura K, Okamoto I, Kashii T, Negoro S, Hirashima T, Kudoh S, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small-cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). *Br J Cancer* 2008;98:907–14.
50. Sequist LV, Martins R, Spigel DR, Grunberg SM, Spira A, Janne P, et al. First-line gefitinib in patients with advanced non-small cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol* 2008;26:2442–9.
51. Morita S, Hirashima T, Hagiwara K, Hida T, Sunaga N, Sugio K, et al. I-CAMP Study Group. Gefitinib combined survival analysis of the mutation positives from the prospective phase II trials (I-CAMP). *J Clin Oncol* 2008;26(Suppl.) (Abstract 8101).
52. Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA^{TM}) monotherapy. Clinical experience in non-small-cell lung cancer. *Drug Saf* 2004;27:1081–92.
53. Fukuoka M, Kris M, Giaccone G, Lynch T, Nakagawa K, Kelly K, et al. Phase II trials of gefitinib ('Iressa', ZD1839): rapid and durable objective responses in patients with advanced non-small-cell lung cancer (IDEAL 1 and IDEAL 2). *Lung Cancer* 2003;41(Suppl. 2):S247–S248 (Abstract P-615).
54. Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008;177:1348–57.
55. Takamochi K, Suzuki K, Bashar AH, Yajima K, Mochizuki T, Itaya T, et al. Readministration of gefitinib in a responder after treatment discontinuation due to gefitinib-related interstitial lung disease: a case report. *J Med Case Reports* 2008;17:138.
56. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–56.
57. Tsuboi M, Le Chevalier T. Interstitial lung disease in patients with non-small-cell lung cancer treated with epidermal growth factor receptor inhibitors. *Med Oncol* 2006;23:161–70.
58. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003;361:137–9.
59. Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol* 2006;24:3657–63.
60. Yoshida S. The results of gefitinib prospective investigation. *Med Drug J* 2005;41:772–89.
61. Nakagawa K, Tamura T, Negoro S, Kudoh S, Yamamoto N, Yamamoto N, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumours. *Ann Oncol* 2003;14:922–30.
62. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002;20:4292–302.
63. Swaisland H, Laight A, Stafford L, Jones H, Morris C, Dane A, et al. Pharmacokinetics and tolerability of the orally active selective epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in healthy volunteers. *Clin Pharmacokinet* 2001;40:297–306.
64. Swaisland HC, Smith RP, Laight A, Kerr DJ, Ranson M, Wilder-Smith CH, et al. Single-dose clinical

pharmacokinetic studies of gefitinib. *Clin Pharmacokinet* 2005;44: 1165–77.
65. Haura E, Sommers E, Becker D, McKillop D, Bepler G. Pilot phase II study of preoperative gefitinib in early stage non-small cell lung cancer with assessment of intratumour gefitinib levels and tumour target modulation. *J Clin Oncol* 2007;25 (Abstract 7603).
66. Guo J, Zhou C, Deng Q, Ren S, Zhang J. Effect of EGFR mutations on gefitinib in advanced previous treated non-small-cell lung cancer. *J Clin Oncol* 2008;26(Suppl.) (Abstract 19132).
67. Sunaga N, Tomizawa Y, Yanagitani N, Iijima H, Kaira K, Shimizu K, et al. Phase II prospective study of the efficacy of gefitinib for the treatment of stage III/IV non-small-cell lung cancer with EGFR mutations, irrespective of previous chemotherapy. *Lung Cancer* 2007;56:383.
68. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, 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 USA* 2004;101:13306–11.
69. Darwish S, Ludovini V, Pistola L, Bianconi F, Betti M, Chiari R, et al. EGFR, KRAS, PIK3CA mutations and response to tyrosine kinase inhibitors (TKIs) in advanced NSCLC patients. *J Clin Oncol* 2008;26(Suppl.) (Abstract 22003).
70. Sasaki H, Endo K, Takada M, Kawahara M, Tanaka H, Kitahara N, et al. EGFR Polymorphism of the Kinase Domain in Japanese Lung Cancer. *J Surg Res* 2007;148:260–3.
71. Nomura M, Shigematsu H, Li L, Suzuki M, Takahashi T, Estess P, et al. Polymorphisms, mutations, and amplification of the EGFR gene in non-small cell lung cancers. *PLoS Med* 2007;4:e125.
72. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, 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: 2129–39.
73. Huang SF, Liu HP, Li LH, Ku YC, Fu YN, Tsai HY, et al. High frequency of epidermal growth factor receptor mutations with complex patterns in non-small cell lung cancers related to gefitinib responsiveness in Taiwan. *Clin Cancer Res* 2004;10:8195–203.
74. Sutani A, Nagai Y, Udagawa K, Uchida Y, Murayama Y, Tanaka T, et al. Phase II study of gefitinib for non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) gene mutations detected by PNA-LNA PCR clamp. Abstract presented at the ASCOAtlantaGA2–6June2006.
75. Douillard JY, Hirsch V, Mok T, Socinski MA, Watkins C, Lowe E, et al. Molecular and clinical subgroup analyses from a phase III trial comparing gefitinib with docetaxel in previously treated non-small cell lung cancer (INTEREST). *J Clin Oncol* 2008;26(Suppl.): abs 8001.
76. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339–46.
77. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–500.
78. Wu JY, Yu CJ, Yang CH, Wu SG, Chiu YH, Gow CH, et al. First or Second-Line Therapy With Gefitinib Produces Equal Survival in Non Small Cell Lung Cancer. *Am J Respir Crit Care Med* 2008
79. Yang CH. EGFR tyrosine kinase inhibitors for the treatment of NSCLC in East Asia: present and future. *Lung Cancer* 2008;60(Suppl. 2):S23–S30.
80. Sasaki H, Okuda K, Takada M, Kawahara M, Kitahara N, Matsumura A, et al. A novel EGFR mutation D1012H and polymorphism at exon 25 in Japanese lung cancer. *J Cancer Res Clin Oncol* 2008;134:1371–6.
81. Bell DW, Brannigan BW, Matsuo K, Finkelstein DM, Sordella R, Settleman J, et al. Increased Prevalence of EGFR-Mutant Lung Cancer in Women and in East Asian Populations: Analysis of Estrogen-Related Polymorphisms. *Clin Cancer Res* 2008;14:4079–84.
82. Kharrat N, Al'Fadhli S, Rebai M, Aifa MS, Kallel I, Khabir A, et al. (AC) dinucleotide repeat polymorphism in intron 1 of human EGFR shows ethnic specificities and high evidence for association with breast cancer. *Int J Biol Markers* 2007;22:258–64.
83. Calvo E, Baselga J. Ethnic differences in response to epidermal growth factor receptor tyrosine kinase inhibitors. *J Clin Oncol* 2006;24:2158–63.
84. Liu W, Innocenti F, Chen P, Das S, Cook EH, Jr, Ratain MJ. Interethnic difference in the allelic distribution of human epidermal growth factor receptor intron 1 polymorphism. *Clin Cancer Res* 2003;9:1009–12.
85. Gebhardt F, Zanker KS, Brandt B. Modulation of epidermal growth factor receptor gene transcription by a polymorphic dinucleotide repeat in intron 1. *J Biol Chem* 1999;274:13176–80.
86. Rosell R, Ichinose Y, Taron M, Sarries C, Queralt C, Mendez P, et al. Mutations in the tyrosine kinase domain of the EGFR gene associated with gefitinib response in non-small-cell lung cancer. *Lung Cancer* 2005;50:25–33.
87. Greulich H, Chen TH, Feng W, Janne P, Alvarez J, Zappaterra M, et al. Oncogenic transformation by inhibitor-sensitive and resistant EGFR mutants. *PLoS Med* 2005;2:1167–76.
88. Okano T, Kondo T, Fujii K, Nishimura T, Takano T, Ohe Y, et al. Proteomic signature corresponding to the response to gefitinib (Iressa, ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor in lung adenocarcinoma. *Clin Cancer Res* 2007;13:799–805.
89. Zucali PA, Ruiz MG, Giovannetti E, Destro A, Varella-Garcia M, Floor K, et al. Role of cMET expression in non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitors. *Ann Oncol* 2008;19:1605–12.
90. Nishimura Y, Yoshioka K, Bereczky B, Itoh K. Evidence for efficient phosphorylation of EGFR and rapid endocytosis of phosphorylated EGFR via the early/late endocytic pathway in a gefitinib-sensitive non-small cell lung cancer cell line. *Mol Cancer* 2008;7:42.
91. Janne PA. Challenges of detecting EGFR T790M in gefitinib/erlotinib-resistant tumours. *Lung Cancer* 2008;60(Suppl. 2):S3–S9.
92. Wang Z, Wu YL, Zhang GC, Zhou Q, Xu CR, Guo AL. EGFR/KRAS mutations and gefitinib therapy in Chinese NSCLC patients. *Onkologie* 2008;31:174–8.
93. Ho C, Murray N, Laskin J, Melosky B, Anderson H, Bebb G. Asian ethnicity and adenocarcinoma histology continues to predict response to gefitinib in patients treated for advanced non-small cell carcinoma of the lung in North America. *Lung Cancer* 2005;49:225–31.
94. Kondo M, Yokoyama T, Fukui T, Yoshioka H, Yokoi K, Nagasaka T, et al. Mutations of epidermal growth factor receptor of non-small cell lung cancer were associated with sensitivity to gefitinib in recurrence after surgery. *Lung Cancer* 2005;50:385–91.
95. Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, 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;23:2513–20.
96. Tokumo M, Toyooka S, Kiura K, Shigematsu H, Tomii K, Aoe M, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. *Clin Cancer Res* 2005;11:1167–73.
97. Hotta K, Kiura K, Toyooka S, Takigawa N, Soh J, Fujiwara Y, et al. Clinical significance of epidermal growth factor receptor gene mutations on treatment outcome after first-line cytotoxic chemotherapy in Japanese patients with non-small-cell lung cancer. *J Thorac Oncol* 2007;2:632–7.
98. Okami J, Taniguchi K, Higashiyama M, Maeda J, Oda K, Orita N, et al. Prognostic factors for gefitinib-treated postoperative recurrence in non-small cell lung cancer. *Oncology* 2007;72:234–42.
99. Takano T, Fukui T, Ohe Y, Tsuta K, Yamamoto S, Nokihara H, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. *J Clin Oncol* 2008;26:5589–95.