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ADIS DRUG EVALUATION

Gefitinib: a review of its use in adults with advanced non-small cell lung cancer

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Abstract Gefitinib (Iressa®) is a selective small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR TKI) indicated for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of *EGFR* tyrosine kinase. Large phase III or IV clinical trials in patients with locally advanced or metastatic NSCLC showed that gefitinib as first- or subsequent-line treatment significantly prolonged progression-free survival (PFS) and improved objective response rates and/or health-related quality of life parameters in patients with activating *EGFR* mutations and in clinically selected patients (e.g., Asian patients or never-smokers) who are more likely to harbour these mutations. Overall survival did not increase significantly with gefitinib, although post-study treatments may have had a confounding effect on this outcome. Gefitinib was generally well tolerated in these studies, with mild or moderate skin reactions, gastrointestinal disturbances and elevations in liver enzymes among the most common adverse reactions in gefitinib recipients; interstitial lung disease has also been reported in <6 % of gefitinib recipients. Compared with chemotherapy, gefitinib as first- or subsequent-line therapy provided similar or greater PFS benefit and was generally associated with fewer haematological adverse events, neurotoxicity, asthenic disorders, as well as grade ≥3 adverse events. Although the position of gefitinib with respect to other EGFR TKIs is not definitively established, current evidence indicates that gefitinib monotherapy is an effective and generally well-tolerated first- or subsequent-line treatment option for patients with NSCLC and activating *EGFR* mutations who have not received an EGFR TKI previously.

Keywords Gefitinib · Epidermal growth factor receptor tyrosine kinase inhibitor · Non-small cell lung cancer

Gefitinib in advanced NSCLC: a summary

Selective EGFR tyrosine kinase inhibitor

First-or subsequent-line treatment with gefitinib improves progression-free survival, objective response rates and/or health-related quality of life parameters in patients with activating *EGFR* mutations

Provides similar or greater benefit than chemotherapy

Generally well tolerated, with some adverse events (e.g. haematological adverse events) occurring less frequently than with chemotherapy

Introduction

Systemic chemotherapy (e.g., platinum-based regimens) has been the mainstay of treatment in advanced non-small cell lung cancer (NSCLC) [1, 2]. However, only moderate clinical benefits and small improvements in long-term survival have been seen

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with these agents [1–3]. Moreover, because of the nonspecific mechanism of action of chemotherapy agents (targeting rapidly dividing cells, including cancer cells and certain normal tissues), these agents are often associated with dose-limiting toxicities [2].

The phenomenon of 'oncogene addiction', whereby some cancers become highly dependent on a specific gene for their survival and proliferation, provided a rationale for targeted therapy in lung cancer [4]. In NSCLC and other epithelial cancers, the epidermal growth factor receptor (EGFR) was identified as a critical oncogene [1]. EGFR, a member of the human epidermal growth factor receptor (HER)/erbB family of transmembrane receptor tyrosine kinases, plays a key role in regulating cell proliferation, migration and differentiation [5, 6]. Dysregulation of EGFR activity by oncogenic mechanisms, such as increased *EGFR* copy number, EGFR protein overexpression and activating gene mutations, is thought to activate downstream signalling pathways (e.g., mitogen-activated protein kinase, mammalian target of rapamycin), which may counteract apoptosis and enhance cellular metabolism and proliferation, resulting in disease [1].

Several approaches have been used to antagonise aberrant EGFR signalling, including monoclonal antibodies that bind to the EGFR extracellular domain and small-molecule tyrosine kinase inhibitors (TKIs) targeting the intracellular EGFR tyrosine kinase domain [7]. Gefitinib (Iressa®) is a selective small-molecule EGFR TKI indicated for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of *EGFR* tyrosine kinase [8]. This article reviews the efficacy and tolerability of gefitinib in this indication and briefly summarises its pharmacology.

Pharmacodynamic properties

The key pharmacodynamic properties of gefitinib are discussed briefly here. The predictors of clinical response to EGFR TKIs [9], mechanisms of drug resistance and potential strategies to overcome resistance [10–12] have been reviewed elsewhere and detailed discussion of these is beyond the scope of this review.

Mechanism of action

Gefitinib, a substituted anilinoquinazoline, reversibly and competitively inhibits the binding of adenosine-5′-triphosphate (ATP) to the tyrosine kinase catalytic domain (half maximal inhibitory concentration of 0.033 μmol/L), thereby blocking signal transduction and resulting in the inhibition of cell proliferation and the induction of apoptosis in cancer cells [13–16].

Gefitinib selectively inhibited epidermal growth factor (EGF)-stimulated tumour cell growth and blocked EGF-stimulated EGFR autophosphorylation in tumour cells in vitro, and dose-dependently inhibited tumour growth in human tumour-derived xenograft models [16]. In vitro, gefitinib inhibited EGFR activation/signalling [17, 18] and affected down-stream receptor-dependent processes in skin from cancer patients (e.g. reduced proliferation and increased apoptosis and the expression of cell-cycle inhibitor $p27^{KIP1}$) [17] and inhibited growth factor production and angiogenesis in human cancer cell lines and xenograft models [19]. The anti-tumour activity of gefitinib was also demonstrated in phase I and II studies in patients with solid malignancies, including NSCLC, colorectal and breast cancer [18, 20–24].

Predictors of efficacy

Despite the evidenced anti-tumour activity of gefitinib, no clear correlation was seen between the level of expression of EGFR and xenograft tumour sensitivity in vitro [16], and tumour responses were observed only in up to 19 % of gefitinib-treated patients with chemotherapy-refractory locally advanced or metastatic NSCLC in phase II clinical studies [23, 24]. It was found that subgroups of patients with NSCLC (never-smokers, Asian patients, females and patients with adenocarcinoma histology) have a higher incidence of specific somatic mutations in the *EGFR* gene that correlate with responsiveness to gefitinib [25–28]. For instance, in one study, somatic *EGFR* mutations were found in eight of nine patients who responded to gefitinib therapy relative to none of the seven patients who did not respond to gefitinib treatment ($p<0.001$) [27]. The relationship between gefitinib efficacy and clinical markers and activating mutations in patients with NSCLC in large pivotal clinical trials is discussed in "Therapeutic Efficacy".

The somatic mutations within the tyrosine kinase domain of *EGFR* are thought to reposition critical amino acids near the ATP cleft, thereby stabilising the interaction between ATP (or its competitor, gefitinib) and the tyrosine kinase domain, resulting in increased receptor activation after ligand binding and enhanced inhibition with gefitinib, which correlates with clinical responsiveness to gefitinib [27]. Many activating (or sensitising) mutations have been discovered, with the four main types being point mutations in exon 18 (G719X, G719S, G719A), in-frame deletions in exon 19, insertions in exon 20 and point mutations in exon 21 (L858R and L861Q) [1, 15, 25, 29]. Exon 19 deletions and the leucine-to-arginine mutation at codon 858 occur most frequently, accounting for ≈90 % of all *EGFR* mutations [1, 15, 25, 29].

In addition to *EGFR* somatic mutations, early clinical studies had indicated that high *EGFR* gene copy number and high EGFR protein expression were associated with clinical benefit [better overall survival (OS) and response] in gefitinib-treated NSCLC patients [30, 31]. However, in large phase III studies, mixed results were seen for high EGFR protein expression; in one study [32], EGFR protein expression was a significant predictor of OS benefit with gefitinib ("Versus Placebo"), but no treatment benefit in terms of OS was seen in other studies [33,

34]. *EGFR* gene copy number was associated with some clinical benefit in gefitinib-treated NSCLC patients in phase III studies [32–34]; however, subsequent analyses of data from one study indicated that this was driven by the coexisting *EGFR* mutation status [34] ("*Versus Carboplatin plus Paclitaxel*"). Other potential molecular predictors of clinical outcomes, including *KRAS* mutations and phosphorylated AKT protein expression, were not related to clinical outcomes in phase III studies [32, 33].

Drug resistance

Although NSCLC patients who have activating *EGFR* mutations experience greater benefit with first-line gefitinib therapy, approximately 30 % of patients with *EGFR*-mutant disease still do not respond to treatment and even patients who initially respond to treatment eventually develop disease progression [12]. Several mechanisms have been proposed for primary resistance to EGFR TKIs (including exon 20 insertions [35] and low expression levels of the pro-apoptotic BH-3 only molecule [36]) and for acquired resistance to EGFR TKIs [including, second-site *EGFR* mutations (e.g. the T790M gatekeeper mutation [37]) and overexpression of mesenchymal epithelial transition factor (MET) [38]].

The T790M mutation and MET amplification are the most common acquired resistance mechanisms, accounting for ≈60 % of cases [11]. Approximately 50 % of EGFR TKI-resistant patients have been found to have the T790M mutation (substitution of threonine to methionine at codon 790, the gatekeeper residue) [11], which is thought to alter the proper binding of the drug to the ATP-binding site of EGFR and restores ATP affinity to the level of wild-type *EGFR* [10, 11, 39]. Overexpression of MET (a transmembrane tyrosine kinase receptor that binds to hepatocyte growth factor) is seen in ≈20 % of patients with acquired resistance [11] and is thought to result in the persistent activation of the downstream phosphoinositide 3-kinase/AKT pathway, thereby overcoming EGFR-induced inhibition [10, 11, 38].

Several strategies to overcome resistance to EGFR TKIs have been examined in preclinical and/or clinical trials, including the use of second-generation (irreversible) EGFR TKIs (e.g. afatinib [40, 41], which may provide inhibition despite the presence of the T790M mutation), combination treatment with drugs (e.g. gefitinib plus the MET TKI crizotinib [42]) and treatment with EGFR TKIs beyond progression [43] (reviewed elsewhere [10–12]). However, no strategy has been approved as yet for the treatment of patients with primary or acquired resistance to gefitinib.

Diagnostic studies

Assessing the *EGFR* mutation status of the patient with a well-validated and robust method (to avoid false negative or false positive determinations) is important [8], as the greatest benefit with gefitinib is seen in patients with activating mutations ("Therapeutic Efficacy"), The historical standard of *EGFR* mutation testing has been direct sequencing of DNA extracted from tumour tissue obtained during biopsy or resection [44]. However, tumour tissue may not be available for many patients, such as patients with advanced disease who may have comorbidities [44, 45]. Therefore, recent research has focussed on defining surrogate sample types for *EGFR* mutation analysis.

A supplementary analysis [46] of the pivotal IPASS clinical study, [47] ("*Versus Carboplatin plus Paclitaxel*") assessed *EGFR* mutation status in previously unanalysed [because of sample quality, type or tumour content (<100 cells)] histology (n=99) and cytology (n=116) samples and suggested that small biopsies and cytology samples can be used for mutation testing. The objective response rates (ORRs) in previously unanalysed *EGFR* mutation-positive histology and cytology samples were found to be consistent with those in previously analysed histology samples (74 and 83 vs. 71 %); the ORRs in corresponding *EGFR* mutation-negative samples were 25 and 16 vs. 1 %. The reduction in tumour size with gefitinib also appeared to be consistent between the previously analysed and unanalysed cytology and histology samples [46].

Another pre-planned exploratory analysis of IPASS suggested that circulating free tumour (cf) DNA from serum samples could also be used for *EGFR* mutation testing [48]. These results were supported by *EGFR* mutation analyses [49] of plasma-derived cfDNA samples from Caucasian patients participating in the IFUM study [50] ("*Versus Cisplatin plus Docetaxel*"). Mandatory tumour and duplicate plasma samples were collected from all eligible patients (n=1033) and several exploratory analyses were performed, including pre-planned comparisons of baseline *EGFR* mutation status of tumour *versus* plasma and between plasma samples, and post hoc assessments of gefitinib efficacy according to tumour and plasma *EGFR* mutation status [49]. Results showed high concordance (94.3 %) between matched tumour and plasma samples, high test specificity (99.8 %) and a test sensitivity of 65.7 % [49]. Mutation status concordance between duplicate baseline plasma samples (regardless of mutation subtype) was also high (96.9 %) [49]. The *EGFR* mutation detection rate was 10.5 % in plasma-derived cfDNA compared with 13.7 % in tumour-derived DNA [49]. Furthermore, patients with *EGFR* mutation-positive cfDNA and those with *EGFR* mutation-positive tumours (regardless of mutation subtype) had similar ORRs (76.9 vs. 69.8 %) and median progression-free survival (PFS; 10.2 vs. 9.7 months) [49]. These results suggest that cfDNA from plasma is a suitable substitute for tumour tissue regardless of mutation subtype; however, tumour tissue should still be considered the preferred sample type when available [49]. The European Medicines Agency recently adopted a positive opinion on a type-II variation to the European label for gefitinib to allow the use of cfDNA for the assessment of *EGFR*

mutation status in NSCLC patients when a tumour sample is not available [8, 51].

Pharmacokinetic properties

The absorption of gefitinib is moderately slow after oral administration, with peak plasma concentrations generally reached at 3–7 h after dose administration [8]. After a single oral dose of 250 mg in cancer patients, the mean absolute bioavailability of gefitinib was 59 %; food was not found to alter gefitinib exposure to a clinically significant extent in healthy volunteers [8]. Once-daily administration of gefitinib results in 2- to 8-fold accumulation of the drug [8], with steady-state plasma concentrations of gefitinib reached after 7–10 doses; circulating plasma concentrations of gefitinib at steady state are usually within a 2- to 3-fold range over the 24 h dosing interval [8]. The concentration of gefitinib in the cerebrospinal fluid (CSF) of lung adenocarcinoma patients was low (mean ratio of CSF to plasma concentration was 1.3 %) and was significantly related to plasma drug concentrations (coefficient of correlation of 0.556; $p=0.006$); gefitinib penetration into CSF was increased significantly by the presence of central nervous system metastases (1.46 vs. 0.95 %; $p=0.042$) [52].

The mean steady-state volume of distribution of gefitinib was 1400 L, which indicates that the drug is extensively distributed into tissue [8]. Gefitinib has a plasma protein binding of ≈90 % and binds to serum albumin and α_1-acid glycoprotein [8].

Gefitinib undergoes extensive oxidative metabolism, largely via cytochrome P450 (CYP) 3A4 and CYP2D6 enzymes [8]. Five metabolites of gefitinib have been identified in the excreta and eight have been identified in the plasma [8]. *O*-desmethyl gefitinib is the major metabolite of gefitinib, which is 14-fold less potent than gefitinib at inhibiting EGFR-stimulated cell growth and does not inhibit tumour cell growth in mice; therefore, it is unlikely to contribute to the clinical activity of gefitinib [8]. In vitro data showed that CYP2D6 was involved in the formation of *O*-desmethyl gefitinib; in a clinical trial in healthy volunteers, the mean exposure to gefitinib was twofold higher in poor metabolizers than in extensive metabolizers of CYP2D6 [8]. Higher gefitinib exposure in poor CYP2D6 metabolizers may be clinically relevant, as the adverse effects of the drug are related to its dose and exposure [8, 53]. Gefitinib is excreted largely in the faeces as metabolites, with <4 % of the administered dose excreted in the urine [8]. In cancer patients, the mean terminal half-life of gefitinib is 41 h and its total plasma clearance is ≈500 mL/min [8].

There was no relationship between the predicted steady-state trough concentration of gefitinib and patient age, bodyweight, gender, ethnicity or creatinine clearance (CL_{CR}, >20 mL/min) in a population pharmacokinetic analysis of data from cancer patients [8]. Caution is advised in patients with CL_{CR} of ≤20 mL/min and patients with moderate or severe hepatic impairment (Child-Pugh B or C) should be closely monitored [8].

Coadministration of gefitinib with docetaxel did not affect the pharmacokinetics of docetaxel in patients with advanced NSCLC [54]. There is a potential for clinically relevant interactions between gefitinib and CYP3A4 inducers (e.g., phenytoin, rifampicin, St John's wort), potent CYP3A4 inhibitors (e.g., ketoconazole, posaconazole clarithromycin), potent CYP2D6 inhibitors and CYP2D6 substrates with a narrow therapeutic index. Substances that cause significant sustained elevation of gastric pH (e.g. proton-pump inhibitors and H_2-antagonists) may reduce the bioavailability and plasma concentrations of gefitinib, resulting in reduced efficacy [8]. However, in two small retrospective studies, concomitant use of antacids did not have a significant effect on the efficacy of gefitinib, as assessed by OS and PFS [55, 56]. In vitro data indicate that gefitinib is a substrate of the membrane transport protein P-glycoprotein (no clinical consequences are expected) and gefitinib inhibits breast cancer resistance protein (the clinical significance of which is unknown) [8]. Local prescribing information should be consulted for further details.

Therapeutic efficacy

This section focuses on data for the approved dosage of gefitinib (250 mg/day; "Dosage and Administration"), based on large ($n>100$) phase III or IV clinical trials. Where assessed, tumour samples were used to determine *EGFR* mutation status by direct sequencing [32, 33, 47, 57, 58] or using targeted *EGFR* mutation tests [e.g. peptide nucleic acid-locked nucleic acid (PNA-LNA) polymerase chain reaction (PCR) clamp and amplification refractory mutation system (ARMS)] [50, 59–62].

In chemotherapy-experienced patients

Versus placebo

The randomised phase III ISEL study was designed to compare OS between patients receiving gefitinib and those receiving placebo, in addition to best supportive care, in unselected patients with locally advanced or metastatic NSCLC who had received at least one platinum-based regimen and were refractory to or intolerant of their latest chemotherapy regimen (Table 1 summarises the key baseline characteristics) [63]. Results showed that gefitinib did not prolong OS to a significant extent relative to placebo either in the overall population or in patients with adenocarcinoma (the most common NSCLC subtype [64]) [coprimary endpoints; Table 2]. However, in the overall population, the median time to

Table 1 Key baseline characteristics of chemotherapy-experienced adults with NSCLC in gefitinib studies

Study (no. of prev chemo)	Percentage of patients			
	Males	Asian	Smoker[a] (no/yes)	Adcr
ISEL (1 to ≥3)	67	20	22/78	48
INTEREST (1–3)	65	22	20/80	54
V-15-32 (1 or 2)	62	100[b]	32/68	78
ISTANA (1)	62	100[b]	41/59	68
KCSG-LU08-01 (1)	15	100[b]	100/0	100
WJOG5108L (≥1)	45	–	–/50	100
ICOGEN (1–3)	58	100[b]	51/49	76

Adcr adenocarcinoma, *chemo* chemotherapy regimens, *prev* previous, – indicates not available

[a] Former/current smoker

[b] Included Japanese (V-15-32, WJOG5108L), Chinese (ICOGEN) and Korean (ISTANA, KCSG-LU08-01) patients

treatment failure (TTF) was significantly prolonged and the ORR was significantly higher with gefitinib than with placebo (Table 2) [63]. Pre-planned subgroup analyses showed that patients who had never smoked and Asian patients had significantly longer median OS and TTF with gefitinib than with placebo (Table 2) [63, 65].

ISEL also examined the relationship between biomarkers (including *EGFR* mutation status, *EGFR* gene copy number and EGFR protein expression) and clinical outcome in gefitinib *versus* placebo recipients [32]. In *EGFR* mutation-positive patients, median OS was not reached with gefitinib [hazard ratio (HR) was not calculated because of few events] and median TTF did not differ significantly between the gefitinib and placebo groups (Table 2); however, the ORR was higher with gefitinib than with placebo (no statistical data available). No significant between-group differences in OS, TTF or ORR were seen in *EGFR* mutation-negative patients (Table 2) [8, 32]. High *EGFR* gene copy number and high EGFR protein expression were also predictors of OS benefit with gefitinib relative to placebo (*p*-values for treatment-by-

Table 2 Efficacy of gefitinib versus placebo in the randomised, open-label, phase III ISEL study in patients with NSCLC who had previously received at least one platinum-based regimen [8, 32, 63, 65]

Population	Treatment[a]	OS		TTF		ORR[b]
(no. of pts)	(no. of pts[c])	Months	HR (95 % CI)	Months	HR (95 % CI)	% pts
Overall (1692)	GEF (1129)	5.6[d]	0.89 (0.77–1.02)[e]	3.0	0.82 (0.73–0.92)**	8.0***
	PL (563)	5.1[d]		2.6		1.3
Adenocarcinoma pts (812)	GEF (541)	6.3[d]	0.84 (0.68–1.03)[e]			
	PL (271)	5.4[d]				
EGFR mutation positive (26)	GEF	NR	NC	10.8	0.79 (0.20–3.12)	37.5
	PL	4.3		3.8		0
EGFR mutation negative (189)	GEF	3.7	1.16 (0.79–1.72)	2.0	1.10 (0.78–1.56)	2.6
	PL	5.9		2.6		0
Never smoker (375)	GEF	8.9	0.67 (0.49–0.92)*	5.6	0.55 (0.42–0.72)***	18.1
	PL	6.1		2.8		0
Smoker (1317)	GEF	5.0	0.92 (0.79–1.06)	2.7	0.89 (0.78–1.01)	5.3
	PL	4.9		2.6		1.6
Asian (342)	GEF (235)	9.5	0.66 (0.48–0.91)*	4.4	0.69 (0.52–0.91)*	12.4
	PL (107)	5.5		2.2		2.1
Non-Asian (1350)	GEF	5.2	0.92 (0.80–1.07)	2.9	0.86 (0.76–0.98)*	6.8
	PL	5.1		2.7		1.0

Median values reported for OS and TTF. Median duration of follow-up was 7.2. Results are for the intent-to-treat population

GEF gefitinib, *NC* not calculated, *NR* not reached, *PL* placebo, *pt(s)* patient(s)

*$p<0.05$; **$p<0.001$; ***$p<0.0001$ vs. PL

[a] Pts received oral GEF 250 mg/day (plus best supportive care) or PL (plus best supportive care)

[b] *p*-value available only for the overall population

[c] Pt numbers in the individual treatment groups are reported where available

[d] Primary endpoint

[e] HRs in additional analyses after a further 3 months follow-up (by which time 70 % of pts had died and ≈9 % of PL recipients had switched to GEF) were 0.89 (0.79–1.01) in the overall population and 0.84 (0.70–1.02) in pts with adenocarcinoma

copy number and treatment-by-protein expression were 0.045 and 0.049) [32].

In terms of health-related quality of life (HR-QOL), there were no significant differences between gefitinib and placebo recipients in the overall population, with both treatment groups experiencing a deterioration in the Functional Assessment of Cancer Therapy-Lung (FACT-L) scores [63]. Lung Cancer Subscale (LCS) scores deteriorated to a significantly ($p=0.019$) lesser extent with gefitinib than with placebo recipients in this population [65]. In post hoc subgroup analyses, gefitinib relative to placebo recipients had significant ($p<0.005$) improvements in FACT-L and LCS scores in patients who had never smoked and in LCS scores in Asian patients [63, 65]. However, the magnitude of difference in LCS scores did not meet the predefined criteria for clinical relevance (increase of ≥2 points from baseline values) in the overall population or in the subgroups [63, 65].

Versus chemotherapy

Versus docetaxel The efficacy of gefitinib was compared with that of docetaxel in three randomised phase III clinical trials (INTEREST [66], V-15-32 [67] and ISTANA [68]) in unselected patients with locally advanced or metastatic [66–68] or recurrent [67] NSCLC who had previously received at least one platinum-based regimen [66–68] (Table 1 summarises the key baseline characteristics).

The results for efficacy outcomes differed between the three studies. In terms of OS, gefitinib was noninferior to docetaxel in the overall population of the INTEREST study [66], but noninferiority between groups was not demonstrated in the V-15-32 study [67] (primary endpoints; Table 3). However, in V-15-32 and in ISTANA, median OS did not differ significantly between gefitinib and docetaxel recipients (Table 3) [67, 68]. Subgroups analyses of data from INTEREST and V-15-32 showed that OS results were generally consistent across patient subgroups based on demographic or baseline characteristics (e.g. age, gender, smoking history) or biomarker status (e.g. *EGFR* gene copy number or mutation status) [66, 67]. In terms of PFS, no significant differences between gefitinib and docetaxel recipients were seen in the overall population of INTEREST and in V-15-32; however, in ISTANA, PFS was significantly prolonged with gefitinib relative to docetaxel (primary endpoint; Table 3). ORRs were

Table 3 Efficacy of oral gefitinib 250 mg/day versus docetaxel in randomised, open-label, phase III clinical trials in patients with locally advanced or metastatic [66–68] or recurrent [67] NSCLC who had previously received platinum-based regimens

Study	Treatment (no. of pts)	OS		PFS		ORR
		Months	HR (95 % CI)	Months	HR (95 % CI)	% pts
INTEREST [66]						
Overall population	GEF (723)	7.6[a, b]	1.02 (0.91–1.15[c])	2.2	1.04 (0.93–1.18)	9.1
	DOC[d] (710)	8.0[a, b]		2.7		7.6
High *EGFR* copy no. [33, 66]	GEF (85)	8.4[a]	1.09 (0.78–1.51)	2.5	0.84 (0.59–1.19)	13.0*
	DOC (89)	7.5[a]		2.8		7.4
EGFR mutation positive [33]	GEF (22)	14.2	0.83 (0.41–1.67)	7.0	0.16 (0.05–0.49)**	42.1*
	DOC (22)	16.6		4.1		21.1
V-15-32 [67]	GEF (245)	11.5[a, e]	1.12 (0.89–1.40[c])	2.0	0.90 (0.72–1.12)	22.5*
	DOC[d] (244)	14.0[a, e]		2.0		12.8
ISTANA [68]	GEF (82)	14.1[f]	0.87 (0.61–1.24)[f]	3.3[a]	0.73 (0.53–0.998)*	28.1**
	DOC[d] (79)	12.2[f]		3.4[a]		7.6

Median values reported for PFS and OS. Median duration of follow-up was 7.6 [66] or 21 [67] months, where reported. Results for the overall population are intent-to-treat [67, 68] or per protocol [66]

DOC docetaxel, *GEF* gefitinib, *pts* patients

*$p<0.05$; **$p\leq0.001$ vs. DOC

[a] Primary endpoint

[b] Noninferiority between groups was demonstrated as the upper limit of the 96 % CI of the HR was <1.154 (predefined criterion)

[c] Values are 96 % CI in INTEREST and 95.24 % CI in V-15-32

[d] Intravenous DOC 75 mg/m^2 (INTEREST, ISTANA) or 60 mg/m^2 (V-15-32) administered every 3 weeks

[e] Noninferiority was not demonstrated as predefined criterion (upper limit of 95.24 % CI of HR ≤1.25) was not met

[f] Results are for the final analysis of OS conducted in February 2009; in a preliminary analysis conducted at the time of PFS assessment (January 2007) the HR for OS was 0.61 (95 % CI 0.35–1.05)

significantly higher with gefitinib than with docetaxel in ISTANA and V-15-32, but not in the overall population of INTEREST (Table 3).

Biomarker analyses conducted in INTEREST showed no significant differences between gefitinib and docetaxel recipients in terms of OS in patients with high *EGFR* gene copy number [therefore, superiority of gefitinib in this subgroup (coprimary endpoint) was not demonstrated; Table 3], in *EGFR* mutation-positive patients (Table 3) or in EGFR protein expression-positive patients (7.9 vs. 6.5 months) [33, 66]. Moreover, no significant treatment-by-subgroup interactions were seen when comparing OS benefit (gefitinib vs. docetaxel) between patients who had *EGFR* high and low copy number, between those who were EGFR protein expression-positive and protein expression-negative, or between patients who were *EGFR* mutation-positive and in patients with the wild-type gene [33].

However, in *EGFR* mutation-positive patients, PFS was significantly prolonged by 2.9 months and the ORR was almost twofold higher with gefitinib than with docetaxel (Table 3) [33, 66]. Patients with high *EGFR* gene copy number also had significantly higher ORR with gefitinib than with docetaxel (Table 3) [33, 66], whereas patients with EGFR protein expression-positive tumours had no significant differences between the gefitinib and docetaxel groups for PFS (1.6 vs. 2.8 months) or ORR (9 vs. 11 %) [33].

HR-QOL was assessed using FACT–L, Trial Outcome Index (TOI) and LCS, with clinically relevant improvements defined as increases from baseline of ≥6 points in FACT-L and TOI scores and ≥2 points in LCS scores for ≥21 days [66, 68] or ≥28 days [67, 69]. Significantly ($p<0.05$) more gefitinib than docetaxel recipients in INTEREST [66] and V-15-32 [67, 69] had sustained and clinically relevant improvements in FACT–L and TOI scores; in ISTANA, there were no significant between-group differences in the proportions of patients with such improvements [68]. In all three studies, the gefitinib and docetaxel groups did not differ significantly in the proportions of patients with clinically relevant symptom improvement, as assessed by the LCS scores [66–68].

Differences between the study populations of these three trials may explain some of the differences in the efficacy outcomes. V-15-32 and ISTANA included only Asian patients [67, 68], whereas INTEREST recruited mostly non-Asian patients [66] (Table 1). Furthermore, in ISTANA, all patients were receiving second-line gefitinib therapy and the proportion of never-smokers (Table 1) and responders (Table 3) was slightly higher than in the other studies [68]. Gefitinib has been associated with better efficacy in never-smokers and in Asian patients ("Versus Placebo") who are also more likely to harbour *EGFR* mutations [25, 70], which may account for the superiority of gefitinib over docetaxel in terms of PFS in ISTANA [68] and the generally longer OS seen in patients in V-15-32 and ISTANA compared with INTEREST [15].

Moreover, post-study treatments may have confounded OS results. In INTEREST, subsequent treatments were generally well balanced; of the gefitinib-treated patients, 31 % switched to docetaxel, 54 % received no systemic therapy other than further EGFR TKI and 15 % received other chemotherapy; of the docetaxel-treated patients, 37 % switched to an EGFR TKI, 53 % received no systemic therapy other that further docetaxel and 10 % received other chemotherapy [66]. By contrast, in V-15-32, the crossover of patients to alternate therapy was greater than initially expected (which may have reduced the statistical power of the study) and the number and type of patients who received these post-study treatments complicated the interpretation of OS results (of the gefitinib-treated patients, 36 % switched to subsequent docetaxel and 40 % received no therapy other than gefitinib; of the docetaxel-treated patients, 53 % switched to subsequent gefitinib and 26 % received no therapy other than docetaxel) [67]. In ISTANA, of the gefitinib-treated patients, 1 % were still receiving randomised gefitinib therapy at the time of analysis, 29.6 % had switched to docetaxel, 24.7 % received no further systemic chemotherapy other than gefitinib, and 44.4 % received other chemotherapy; of the docetaxel-treated patients, 67.1 % switched to an EGFR TKI, 26.3 % received no further systemic chemotherapy other than docetaxel and 6.6 % received other chemotherapy [68].

Versus pemetrexed The randomised, phase III KCSG-LU08-01 study compared the efficacy of gefitinib with that of pemetrexed as second-line therapy in clinically selected (never-smokers with advanced pulmonary adenocarcinoma) Korean patients with locally advanced NSCLC treated with one previous platinum-based regimen [57]. Gefitinib as second-line therapy significantly prolonged median PFS (primary endpoint) by 6 months relative to treatment with pemetrexed, corresponding to a 46 % reduction in the risk of progression or death (Table 4). The ORR was also significantly higher with gefitinib than with pemetrexed; however, OS did not differ significantly between the two treatment groups (Table 4). The study authors suggested that the lack of survival benefit with gefitinib may be because of the high (83.8 %) post-study treatment rate (including 61.2 % of pemetrexed-treated patients who switched to third-line treatment with gefitinib), which may offset the between-group difference in PFS [57].

Exploratory biomarker analyses showed significant PFS benefit with gefitinib relative to pemetrexed in *EGFR* mutation-positive patients, but not in *EGFR* mutation-negative patients (Table 4) [57]. The ORR was also significantly higher in gefitinib-treated *EGFR* mutation-positive relative to mutation-negative patients (Table 4) [57]. HR-QOL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and results showed that the global health status and functional scale scores did not differ

Table 4 Efficacy of gefitinib versus pemetrexed in a randomised, open-label, phase III clinical trial in patients who had never smoked and who had locally advanced or metastatic (stage IIIB or IV) pulmonary adenocarcinoma treated with just one previous platinum-based regimen

Study	Treatment[a] (no. of pts)	PFS		OS		ORR[b]
		Months	HR (95 % CI)	Months	HR (95 % CI)	% pts
KCSG-LU08-01 [57]	GEF (68)	9.0[c]	0.54 (0.37–0.79)**	22.2	0.80 (0.50–1.30)	58.8**
	PEM (67)	3.0[c]		18.9		22.4
EGFR mutation positive	GEF (16)	15.7	0.30 (0.13–0.72)*			87.5†
	PEM (17)	2.9				
EGFR mutation negative	GEF (18)	5.9	0.56 (0.28–1.13)			38.0
	PEM (20)	2.7				

Median values reported for PFS and OS. Median follow-up duration was 15.9 months. Results are for the evaluable population

GEF gefitinib, *PEM* pemetrexed, *pts* patients

*$p \leq 0.005$; **$p < 0.001$ vs. PEM; † $p = 0.004$ vs. *EGFR* mutation positive

[a] Oral GEF 250 mg/day or intravenous PEM 500 mg/m^2 on day 1 of a 3-weekly cycle

[b] Investigator-assessed values; ORR as assessed by independent review was 45.6 % in GEF versus 28.4 % in PEM recipients ($p = 0.038$)

[c] Primary endpoint

significantly between gefitinib and pemetrexed recipients. Except for significantly ($p < 0.01$) lower dyspnoea scores with gefitinib (18.9 vs. 35.6) and diarrhoea scores with pemetrexed (6.1 vs. 14.4), the two treatment groups did not differ significantly in the symptom scales [57].

Versus other EGFR TKIs

The phase III WJOG5108L study compared the efficacy of gefitinib with that of erlotinib in patients with advanced lung adenocarcinoma (stage IIIB/IV) or recurrent disease who had previously received ≥1 chemotherapy regimen (abstract presentation) [71]. Results showed that although noninferiority between gefitinib and erlotinib for PFS was not demonstrated (primary endpoint), the two treatment groups did not differ significantly in terms of efficacy endpoints (Table 5) [71]. These findings were supported by an earlier phase II study in clinically selected (having *EGFR* mutation or ≥2 clinical factors) Korean patients with locally advanced or metastatic stage IIIB or IV NSCLC who had failed first-line chemotherapy [72]. In exploratory analyses, gefitinib and erlotinib recipients did not differ significantly

Table 5 Efficacy of gefitinib versus that of other targeted therapies in randomised, open-label, phase III clinical trials in Asian patients with stage IIIB/IV NSCLC [59] or advanced (stage IIIB/IV or recurrent) lung adenocarcinoma [71] who had failed previous chemotherapy

Study	Treatment[a] (no. of pts)	PFS		OS		ORR
		Months	HR (95 % CI)	Months	HR (95 % CI)	% pts
WJOG5108L [71]	GEF (279)	6.5[b, c]	1.13 (0.94–1.35)	22.8	1.04 (0.83–1.29)	46.1
	ERL (280)	7.5[b, c]		24.5		43.9
EGFR mutation positive	GEF (186)	8.9		26.6		
	ERL (185)	10.1		32.0		
ICOGEN [59]	GEF (196)	3. 4[b, d]	0.84 (0.67–1.05)	13.9	1.02 (0.82–1.27)	27.2
	ICO (199)	4.6[b, d]		13.3		27.6
EGFR mutation positive	GEF (39)	5.3	0.78 (0.42–1.28)	20.2	1.10 (0.61–1.96)	53.8
	ICO (29)	7.8		20.9		62.1

Median values reported for PFS and OS. Results are for the full analysis set [59], where reported. One study [71] is available as an abstract

ERL erlotinib, *GEF* gefitinib, *ICO* icotinib, *NR* not reached, *pts* patients

[a] Oral GEF 250 mg once daily, oral ERL 150 mg once daily or oral ICO 125 mg thrice daily (ICO is approved for use only in China)

[b] Primary endpoint

[c] Noninferiority between groups was not demonstrated as the upper CI limit was not <1.30 (predefined criterion)

[d] Noninferiority between groups was demonstrated as the upper limit of the 95 % CI for HR was <1.14 (predefined noninferiority criterion)

in terms of PFS (4.9 vs. 3.1 months) or ORR (47.9 vs. 39.6 %), while median OS was not reached in either treatment group [72].

Another phase III study compared the efficacy of gefitinib with that of icotinib (approved for use only in China) in Chinese patients with locally advanced or metastatic stage IIIB or IV NSCLC who had disease progression after ≥1 platinum-based chemotherapy regimen. Icotinib was found to be noninferior to gefitinib in terms of PFS (primary endpoint) and the two treatment groups did not differ significantly in OS and ORR (Table 5) [59]. Across both treatment groups, patients with activating *EGFR* mutations had significantly ($p<0.0001$) longer median PFS (6.3 vs. 2.3 months; HR 0.44; 95 % CI 0.31–0.63) and OS (HR 0.59; 95 % CI 0.26–0.57) than patients with wild-type mutations. Among patients with activating *EGFR* mutations, there were no significant differences between the gefitinib and icotinib groups for PFS, OS and ORRs (Table 5) [59].

In chemotherapy-naïve patients

Previous studies had shown greatest clinical benefit of gefitinib in women, in patients who had never smoked, had pulmonary adenocarcinomas or who were of Asian origin [23, 24, 63, 73]. These populations have also been associated with a relatively high incidence of somatic mutations in the region of the *EGFR* gene encoding for the tyrosine kinase domain [25, 70]. Therefore, several trials were conducted to evaluate the efficacy of gefitinib as first-line treatment in a previously untreated patient population enriched for these biological factors ("In Clinically Selected Patients"), as well as in patients with activating *EGFR* mutations ("In Patients with Activating EGFR Mutation").

In clinically selected patients

Two randomised phase III trials, the IPASS [47] and First-SIGNAL [58], compared the efficacy of gefitinib *versus* chemotherapy (carboplatin plus paclitaxel or gemcitabine plus cisplatin) in previously untreated patients in East Asia who had stage IIIB or IV pulmonary adenocarcinoma and who were non-smokers or former light smokers (Table 6 summarises the key baseline characteristics). The role of *EGFR* mutation as a predictor of the efficacy of gefitinib or chemotherapy was also assessed in these studies [47, 58].

Versus carboplatin plus paclitaxel In the IPASS study, after establishing the noninferiority of gefitinib *versus* carboplatin plus paclitaxel in terms of median PFS (primary endpoint), gefitinib initial therapy was found to be superior to chemotherapy in previously untreated patients with advanced pulmonary adenocarcinoma, as indicated by a 26 % reduction in the risk of disease progression or death (Table 7) [47]. The

Table 6 Key baseline characteristics of chemotherapy-naïve adults with NSCLC in gefitinib studies

Study (ethnic group)	Percentage of patients		
	Females	Smoker[a] (no/yes)	Adcr
IPASS (East Asian)	79	94[b]/6	96
First-SIGNAL (Korean)	89	100/0	100
NEJ002 (Japanese)	64	62/38	93
WJTOG3405 (Japanese)	69	69/31	97
IFUM (Caucasian)	71	64/36	97
Inoue et al. (Japanese) [62]	79	76/24	93

Adcr adenocarcinoma

[a] Former/current smoker

[b] Smoked <100 cigarettes

Kaplan-Meier PFS curves for gefitinib and chemotherapy crossed at approximately 6 months, favouring chemotherapy during the first 6 months and gefitinib during the following 16 months of treatment. At 12 months, the PFS rate was approximately fourfold higher in gefitinib than in chemotherapy recipients (24.9 vs. 6.7 %). Furthermore, pre-planned subgroup analyses showed that with the exception of age, no significant subgroup-by-treatment interactions were seen in PFS analyses in patients stratified according to demographic and baseline characteristics (e.g. age, gender, smoking history), suggesting a benefit with gefitinib across a broad patient population. With regard to age, greater benefit with gefitinib was seen in patients aged ≥65 years (HR for progression or death 0.58; 95 % CI 0.45–0.76) relative to those aged <65 years (HR 0.81; 95 % CI 0.70–0.95) (p-value for interaction=0.03) [47].

In terms of secondary endpoints, ORR was significantly higher in gefitinib than in chemotherapy recipients (Table 7) [47]. However, there was no significant difference between the gefitinib and chemotherapy groups in OS in an early analysis conducted at the time of PFS analysis [47], as well as in the final analysis (Table 7) [34]. In terms of HR-QOL, significantly ($p<0.05$) more gefitinib than chemotherapy recipients experienced clinically relevant improvements in FACT–L and TOI scores; however, there was no significant difference between the two treatment groups in clinically relevant improvement in symptoms, as assessed by the LCS scores [47]. Clinically relevant improvements were defined as increases from baseline of ≥6 points in FACT-L and TOI scores and ≥2 points in LCS scores for ≥21 days [47].

A pre-planned biomarker analysis in 437 evaluable patients found *EGFR* mutation status to be the strongest predictor of the effect of gefitinib on PFS [34, 47]. A significant ($p<0.001$) interaction between treatment and *EGFR* mutation status was seen for PFS, with significantly longer PFS in gefitinib than

Table 7 Efficacy of oral gefitinib 250 mg/day as first-line therapy in randomised, open-label, phase III studies in clinically selected[a] chemotherapy-naïve patients with stage IIIB or IV pulmonary adenocarcinoma. Results for the overall population are intent-to-treat

Study	Treatment[b] (no. of pts)	PFS		OS[c]		ORR
		Months	HR[d] (95 % CI)	Months	HR[d] (95 % CI)	% pts
IPASS [8, 47]						
Overall population	GEF (609)	5.7[e, f]	0.74 (0.65–0.85)**	18.8	0.90 (0.79–1.02)	43.0**
	CAR + PAC (608)	5.8[e, f]		17.4		32.2
EGFR mutation positive	GEF (132)	9.5	0.48 (0.36–0.64)**	21.6	1.00 (0.76–1.33)	71.2**
	CAR + PAC (129)	6.3		21.9		47.3
EGFR mutation negative	GEF (91)	1.5	2.85 (2.05–3.98)**	11.2	1.18 (0.86–1.63)	1.1
	CAR + PAC (85)	5.5		12.7		23.5**
First-SIGNAL [58]						
Overall population	GEF (159)	5.8	1.198 (0.94–1.52)	22.3[e]	0.93 (0.72–1.21)	55.4
	GEM + CIS (150)	6.4		22.9[e]		46.0
EGFR mutation positive	GEF (26)	8.0	0.54 (0.27–1.10)	27.2	1.04 (0.5–2.18)	84.6*
	GEM + CIS (16)	6.3		18.4		37.5
EGFR mutation negative	GEF (27)	2.1	1.42 (0.82–2.47)	25.6	1.00 (0.52–1.91)	25.9
	GEM + CIS (27)	6.4		21.9		51.9

Median values reported for PFS and OS. Median follow-up duration was 5.6 months (or 17 months for OS) [47] or 35 months [58]

CAR carboplatin, *CIS* cisplatin, *GEF* gefitinib, *GEM* gemcitabine, *PAC* paclitaxel, *pts* patients

*p=0.002, **p≤0.001 vs. comparator

[a] IPASS included East Asian never-smokers or former light smokers, and first-SIGNAL included Korean never smokers

[b] GEF + intravenous PAC 200 mg/m^2 plus CAR at an area under the concentration-time curve of 5 or 6 mg/mL/min on day 1 in 3-weekly cycles for ≤6 cycles, or GEF + intravenous GEM 1250 mg/m^2 on days 1 and 8 plus intravenous CIS 75 mg/m^2 on day 1 in 3-weekly cycles for ≤9 cycles

[c] OS was assessed when 954 (78 %) pts had died in IPASS and 224 (71.8 %) pts had died in First-SIGNAL

[d] HR of <1 indicates that GEF is favoured over CAR + PAC and an HR of >1 indicates that CAR + PAC is favoured over GEF

[e] Primary endpoint

[f] Noninferiority between treatment groups was demonstrated as the 95 % CI of the HR was <1.2 (predefined noninferiority limit)

chemotherapy recipients in mutation-positive patients (52 % reduction in the risk of progression of death) and significantly shorter PFS with gefitinib than with chemotherapy in mutation-negative patients (Table 7) [34, 47]. The contrasting results in *EGFR* mutation-positive *versus* mutation-negative patients may explain the crossing over of the Kaplan-Meir PFS curves, with the mutation-negative group accounting for the initial benefit of chemotherapy over gefitinib, and the mutation-positive group explaining the subsequent benefit of gefitinib over chemotherapy [47].

In the mutation-positive subgroup, ORR was significantly higher (Table 7) and significantly (p<0.001) more patients had clinically relevant improvements in FACT-L, TOI and LCS scores with gefitinib than with chemotherapy [47, 74]. By contrast, in the mutation-negative group, ORR was significantly lower (Table 7) and clinically relevant improvements in these HR-QOL parameters were seen in significantly (p<0.05) fewer gefitinib than chemotherapy recipients [47, 74]. However, OS did not differ significantly between the two treatment groups in the mutation-positive or mutation-negative groups (Table 7; p-value for the interaction was 0.48) [34]. It was thought that OS results may have been confounded by subsequent treatments that patients received; of *EGFR* mutation-positive patients, 64.3 % of patients randomly assigned to carboplatin plus paclitaxel subsequently received EGFR TKIs [34].

In addition to *EGFR* mutation status, high *EGFR* gene copy number was also found to be a predictive biomarker of the effect of gefitinib *versus* chemotherapy on PFS (p-value for the treatment-by-gene copy number interaction was 0.044) [34]. However, post hoc analyses showed that this effect was driven by the coexisting *EGFR* mutation status; in *EGFR* mutation-positive patients, PFS was significantly longer with gefitinib than with chemotherapy regardless of whether patients had high (HR 0.48; 95 % CI 0.34–0.67) or low (HR 0.51; 95 % CI 0.25–1.04) *EGFR* gene copy number. EGFR protein expression was not predictive of benefit with gefitinib [34].

Another pre-planned analysis evaluated the efficacy of gefitinib in patients recruited in China and showed that PFS in Chinese patients was similar to that in the overall population (p-value for the treatment-by-country interaction=0.427) [75].

Probably because of small patient numbers, PFS results in the subgroups of patients stratified according to *EGFR* mutation status (n=87) or gene copy number (n=84) favoured chemotherapy over gefitinib and, therefore, were not consistent with results in the overall population [75].

Post hoc analyses of IPASS in patients who responded (complete or partial response according to the Response Evaluation Criteria In Solid Tumours) to gefitinib therapy showed that the median time to response was 6.1 weeks and the median duration of response was 9.7 months in the overall population (n=262), and 6.0 weeks and 8.7 months, respectively in the *EGFR* mutation-positive population (n=94) [76]. Patients in the overall population who responded to gefitinib had significant tumour shrinkage (as assessed by the percentage decrease from baseline in tumour size), with the greatest magnitude of shrinkage seen in the mutation-positive subgroup, according to waterfall plots. Moreover, tumour progression was found to be associated with worsening of HR-QOL; at 4 months after randomization, approximately twice as many patients whose tumours progressed with gefitinib experienced clinically relevant deterioration in HR-QOL (defined as worsening of ≥6-points in FACT-L or TOI scores and ≥2-points in LCS scores for ≥21 days) compared with patients whose tumours did not progress [76].

Versus gemcitabine plus cisplatin The First-SIGNAL study did not demonstrate the superiority of gefitinib over gemcitabine plus cisplatin in terms of OS (primary endpoint) in chemotherapy-naïve Korean never-smokers with advanced pulmonary adenocarcinoma (Table 7) [58], as OS did not differ significantly between the two treatment groups. The 1-year survival rates in gefitinib and chemotherapy recipients were 74.2 *versus* 76.2 % and the 2-year rates were 47.7 *versus* 47.4 %. Of note, 75 % of chemotherapy-treated patients had switched to treatment with an EGFR-TKI after discontinuing study treatment, which may have confounded OS results [58]. Median PFS and ORRs also did not differ significantly between gefitinib and chemotherapy recipients (Table 7); however, PFS rates with gefitinib at 1 year were ≈6-fold higher (16.7 vs. 2.8 %) and the rates at 2 years were ≈2-fold higher (3.2 vs. 1.4 %) than with chemotherapy. As in the IPASS study, the PFS curves favoured chemotherapy during the first 7 months and gefitinib thereafter, with a crossover seen at 7 months [58].

In biomarker analyses, with the exception of significantly higher ORRs with gefitinib than with chemotherapy in *EGFR* mutation-positive patients, no significant between-group differences in efficacy outcomes were seen in the mutation-positive or -negative patients (Table 7) [58]. However, in gefitinib recipients (but not in chemotherapy recipients), the *EGFR* mutation-positive status was significantly (p<0.001 vs. mutation-negative status) predictive of longer PFS (HR 0.38; 95 % CI 0.21–0.67) and higher ORRs (84.6 vs. 25.9 %) [58].

In patients with activating EGFR mutations

In chemotherapy-naïve patients with NSCLC who had activating *EGFR* mutations, a significant benefit of gefitinib over chemotherapy (carboplatin plus paclitaxel or cisplatin plus docetaxel) was seen in two randomised phase III studies in Japanese patients (NEJ002 [60] and WJTOG3405 [61]), with results from the open-label phase IV IFUM study confirming its efficacy in Caucasian patients [50] (Table 8). In addition, benefit of gefitinib therapy was also seen in a small phase II study in patients with activating *EGFR* mutations and a poor performance status (PS) according to Eastern Cooperative Oncology Group criteria [62]. Patients included in these studies were required to have advanced NSCLC with activating *EGFR* mutation [50, 60–62], with three of the studies excluding patients with resistant *EGFR* mutations (e.g. T790M) [50, 60, 62]. Patients included in the phase II study were also required to have an estimated life expectancy of <4 months with best supportive care alone [62]. Table 6 summarises other key baseline characteristics of patients in these studies.

Versus carboplatin plus paclitaxel Initial therapy with gefitinib significantly prolonged median PFS by 4.9 months (primary endpoint) relative to carboplatin plus paclitaxel in a prespecified interim analysis of the NEJ002 study [60], with the benefit of gefitinib maintained in the final and updated PFS analyses [77] (Table 8). The 1-year PFS rates in gefitinib and chemotherapy recipients were 42.1 and 8.4 %, and the 2-year rates in the respective groups were 3.2 and 0 % [60]. In addition, the ORR was significantly higher (approximately twofold) with gefitinib than with chemotherapy (interim analysis) [60]; however, OS did not differ significantly between the treatment groups at any timepoint [60, 77] (Table 8).

HR-QOL was assessed using the Care Notebook (a validated, self-administered cancer-specific, 11-point questionnaire) and results showed that patients receiving gefitinib had significantly (p<0.0001) longer time to 9.1 % deterioration in pain and shortness of breath and daily functioning than patients receiving chemotherapy in the primary HR-QOL analysis at 20 weeks [79]. Gefitinib recipients also had significantly (p<0.0001) longer times to severe (27.3 %) deterioration in pain and shortness of breath and daily functioning. In addition, the time to 27.3 % deterioration (but not 9.1 % deterioration) in anxiety was significantly (p=0.01) longer with gefitinib than with chemotherapy. Gefitinib was superior (p<0.0001) to chemotherapy on the physical and life well-being scales, but there was no significant between-group difference on the mental well-being scale [79].

Versus cisplatin plus docetaxel First-line gefitinib significantly prolonged median PFS by 2.9 months relative to cisplatin plus docetaxel (primary endpoint) in the initial analysis of the WJTOG3405 study, which corresponded to a 51 % reduction

Table 8 Efficacy of oral gefitinib 250 mg/day in randomised, open-label, phase III trials and a single-arm phase IV trial in chemotherapy-naïve patients with NSCLC and activating *EGFR* mutations

Study	Treatment (no. of pts)	PFS		OS		ORR
		Months	HR (95 % CI)	Months	HR (95 % CI)	% pts
NEJ002[a]						
Interim analysis [60, 77]	GEF (114)	10.4[a, b]	0.36 (0.25–0.51)*	30.5	0. 8 (0.52–1.23)	73.7*
	CAR + PAC[c] (114)	5.5[a, b]		23.6		30.7
Updated analysis [77]	GEF	10.8	0.32 (0.24–0.44)*	27.7	0.9 (0.63–1.24)	
	CAR + PAC[c]	5.4		26.6		
WJTOG3405 [d]						
Initial analysis [61]	GEF (86)	9.2[b]	0.49 (0.34–0.71)*	30.9[e]	1.64 (0.75–3.58)	62.1*
	CIS + DOC[c] (86)	6.3[b]		NR[e]		32.2
Updated analysis [78]	GEF			36	1.19 (0.77–1.83)	
	CIS + DOC[c]			39		
IFUM[f] [50]	GEF (106)	9.7		19.2		69.8[b]

Median values reported for PFS and OS. Results are ITT (NEJ002), modified ITT (WJTOG3405) or full analysis set (IFUM)

CAR carboplatin, *CIS* cisplatin, *DOC* docetaxel, *GEF* gefitinib, *ITT* intent-to-treat, *NR* not reached, *PAC* paclitaxel, *pts* patients

*$p<0.001$ vs. comparator

[a] A pre-planned interim analysis was conducted at a median follow-up of 17.6 months [60], the final PFS analysis in December 2009 (median follow-up not reported) [60] and updated, unplanned OS and PFS analyses at a median follow-up of 23 months [77]. In the final PFS analysis, median PFS was 10.8 months with GEF and 5.4 months with CAR + PAC (HR 0.30; 95 % CI 0.22–0.41; $p<0.001$)

[b] Primary endpoint

[c] Intravenous PAC 200 mg/m^2 plus intravenous CAR at a dose equivalent to an area under the concentration-time curve of 6 mg/mL/min on day 1 in 3-weekly cycles, or intravenous DOC 60 mg/m^2 plus intravenous CIS 80 mg/m^2 on day 1 of 3-weekly cycles for 1–6 cycles

[d] The median follow-up duration was 2.7 months for the initial analysis [61] and 34 months for the updated analysis (abstract) [78]

[e] Data for OS were immature

[f] Median follow-up duration of 13.0 months

in the risk of disease progression or death [61]. Gefitinib recipients also had significantly ($p\leq0.02$) higher ORRs (approximately twofold; Table 8) and disease control rates (93.1 vs. 78.0 %) than chemotherapy recipients [61]. However, OS did not differ significantly between the treatment groups at the time of initial [61] or updated analyses (abstract presentation) [78] (Table 8).

In Caucasian patients with activating EGFR mutations

As efficacy data for gefitinib first-line therapy had been assessed only in Asian populations, the IFUM study undertook to confirm its efficacy in *EGFR* mutation-positive Caucasians and showed that the ORR (primary endpoint), PFS and OS in these patients were generally similar to those seen previously in Asian patients (Table 8) [50]. Subgroup analyses showed that the ORR was consistent across patient subgroups based on demographic and baseline characteristics (e.g. age, gender, smoking history), indicating that the benefit of treatment was seen across a broad patient population. The 1-year PFS rate was 38.5 % and the disease control rate was 90.6 % with gefitinib treatment [50].

In patients with poor performance status and activating EGFR mutations

A small ($n=29$ evaluable) phase II study showed that treatment with gefitinib was beneficial in patients with activating *EGFR* mutations and poor PS, including 22 patients who had a PS of 3 or 4 because of various cancer-related conditions [62]. After a median follow-up of 17.8 months, the ORR (primary endpoint) and disease control rates in gefitinib recipients were 66 and 90 %, respectively, and the median PFS and OS were 6.5 and 17.8 months. Moreover, 79 % of patients had an improvement in PS following gefitinib therapy ($p<0.00005$), with 68 % of patients experiencing an improvement from a PS of 3 or 4 at baseline to a PS of 0 or 1, which was considered clinically valuable [62].

Real-world evidence

Although randomised clinical studies have not shown a benefit with gefitinib in terms of OS, which may at least partly be because of the confounding effect of post-study treatments, real-world evidence suggests a survival benefit with gefitinib [12]. One study conducted in Japan compared OS

between patients with advanced lung adenocarcinoma who began first-line systemic therapy before gefitinib approval (January 1999 to July 2001; n=200) with those who started treatment after gefitinib approval (July 2002 to December 2004; n=130) [80]. In patients with activating *EGFR* mutations (136 of 330 patients), OS was found to be significantly longer in patients who were treated after gefitinib approval than in those treated before gefitinib approval (median 27.2 vs. 13.6 months; p<0.001), with a significant interaction seen between *EGFR* mutation status and OS (p=0.045) [80]. No significant between-group difference in OS was seen in patients without activating *EGFR* mutations (median 13.2 vs. 10.4 months) [80].

Similar benefit with gefitinib was also seen in a matched-pair case-control study in patients with advanced/metastatic or recurrent NSCLC in Korea. Median OS was found to be significantly longer in patients in the post-gefitinib era (January 2002 to December 2005; n=334) than in those in the pre-gefitinib era (January 1999 to December 2001; n=334) (19.3 vs. 11.5 months; p<0.001), with a significant association seen between gefitinib and prolongation of OS (HR 0.58; 95 % CI 0.49–0.68; p<0.001) [81].

Tolerability

General profile

Gefitinib was generally well tolerated in patients with locally advanced or metastatic NSCLC. In the placebo-controlled ISEL study, the majority of patients in the gefitinib and placebo groups experienced at least one adverse event (82 vs. 71 %), with any-grade rash (37 vs. 10 %), diarrhoea (27 vs. 9 %), nausea (17 vs. 16 %), anorexia (17 vs. 14 %), vomiting (14 vs. 10 %), dry skin (11 vs. 4 %) and constipation (10 vs. 13 %) occurring most frequently (incidence ≥10 %) in gefitinib recipients [63]. There were no clinically relevant differences between the gefitinib and placebo groups in the incidences of grade 3 or 4 adverse events (30 vs. 27 %) or serious adverse events (19 vs. 17 %) [82]; the most common grade 3 or 4 adverse events in gefitinib recipients were diarrhoea (3 vs. 1 % of placebo), asthenic conditions (3 vs. 3 %), dyspnoea (3 vs. 4 %) and pneumonia (3 vs. 3 %) [63]. The adverse event-related withdrawal rates in gefitinib and placebo recipients were 5 % and 2 %, dose interruptions because of adverse events were required in 11 and 5 % of patients, and 5 and 4 % of patients died as a result of adverse events [63].

There were no clinically relevant changes in haematological variables in ISEL, with gefitinib recipients experiencing generally mild to moderate and asymptomatic elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and a small number of patients having mild increases in blood creatinine levels [63]. The tolerability profile of gefitinib in Asian patients (n=342) was generally similar to that of the overall population, with at least one adverse event reported in 97 % of gefitinib and 86 % of placebo recipients, and grade 3 or 4 adverse events reported in 43 and 36 % of patients, respectively [63].

In pooled data from the three large phase III trials, ISEL, INTEREST and IPASS, the most common adverse reactions (incidence >10 %) with gefitinib were skin reactions (including rash, acne, dry skin and pruritus; 57.9 %), diarrhoea (34.9 %), anorexia (19.7 %), nausea (17.8 %), asthenia (17.7 %), vomiting (13.8 %), stomatitis (11.0 %) and elevations in ALT levels (10.1 %) [8, 82]. Most adverse reactions were mild or moderate in severity, occurred usually during the first month of treatment and were generally reversible [8, 82]. Severe adverse reactions (grade 3 or 4) were reported in ≈8 % of gefitinib recipients, with ≈3 % of patients discontinuing treatment because of an adverse reaction [8].

In addition to the usually mild to moderate increases in ALT, AST or bilirubin levels, there have been uncommon reports of hepatitis (including isolated cases of hepatic failure, with fatal outcomes in some instances) in gefitinib recipients [8]. Therefore, periodic monitoring of liver function is recommended for patients receiving gefitinib therapy and treatment discontinuation may be required in some patients [8].

Versus chemotherapy

The nature of adverse events with gefitinib and chemotherapy was generally similar across chemotherapy trials, with skin-related adverse events, diarrhoea and liver function abnormalities more common with gefitinib, and haematological adverse events, neurotoxicity, asthenic disorders and alopecia more common with chemotherapy [47, 58, 60, 61, 66–68]. For example, in the large INTEREST trial comparing gefitinib with docetaxel in chemotherapy-experienced patients, rash or acne (49 vs. 10 %) and diarrhoea (35 vs. 25 %) were the most frequent (incidence >20 %) adverse events with gefitinib, while neutropenia (74 vs. 5 %), asthenic disorders (47 vs. 25 %), alopecia (36 vs. 3 %), nausea (26 vs. 20 %) and neurotoxicity (24 vs. 7 %) occurred most commonly with docetaxel (all p<0.01) [66]. In the IPASS study in chemotherapy-naïve patients, significantly (p<0.0001) more gefitinib than docetaxel recipients had rash or acne (65.6 vs. 22.4 %), diarrhoea (45.1 vs. 21.7 %) and grade ≥3 elevations in liver transaminase levels (9.4 vs. 1.0 %), while significantly (p≤0.0001) more docetaxel than gefitinib recipients had neurotoxicity (69.8 vs. 4.9 %), nausea (44 vs. 12 %), vomiting (32.8 vs. 9.7 %) and grade ≥3 neutropenia (65.4 vs. 0.7 %), leukopenia (34.3 vs. 0.2 %), anaemia (9.5 vs. 1.8 %) and thrombocytopenia (4.9 vs. 0.8 %) [47].

In the KCSG-LU08-01 study, the tolerability profile of gefitinib was as expected, with acneiform rash (45.6 vs. 4.5 %),

pruritus (30.9 vs. 9.0 %) and diarrhoea (26.5 vs. 4.5 %) reported more frequently with gefitinib than with pemetrexed [57]. Consistent with the findings that pemetrexed has a better tolerability profile than that of docetaxel [83], haematological adverse events were rare with both gefitinib and pemetrexed (≤1.5 % of patients had neutropenia or thrombocytopenia in either treatment group) [57].

Across chemotherapy trials, the incidences of grade ≥3 adverse events were generally lower with gefitinib than with chemotherapy (29–41 % vs. 56–72 %) [47, 58, 60, 61, 66–68]. In addition, where reported, approximately half as many gefitinib recipients had dose interruptions or delays compared with docetaxel (26 vs. 52 % in V-15-32; 5 vs. 17 % in ISTANA) or carboplatin plus paclitaxel (16 vs. 35 % in IPASS). There were few reports of adverse event-related deaths with gefitinib or chemotherapy (0–5 % vs. 0–4 %).

Versus other EGFR TKIs

In the phase III WJOG5108L study comparing gefitinib with erlotinib, numerically fewer gefitinib than erlotinib recipients had grade 3 or 4 rash (2.2 vs. 18.1 %) and numerically more gefitinib than erlotinib recipients had grade 3 or 4 elevations in AST (6.1 vs. 2.2 %) or ALT (13.0 vs. 3.3 %) levels [71]. In a phase II study, the most frequent treatment-related adverse events with gefitinib and erlotinib were any-grade skin rash (63 vs. 73 %) and diarrhoea (33 vs. 36 %); however, gefitinib recipients had numerically lower incidences of grade 2 or 3 skin rash (10 vs. 44 %) and any-grade fatigue (0 vs. 17 %) than erlotinib recipients [72].

The nature of treatment-related adverse events was similar between gefitinib and icotinib recipients, with any-grade rash (49 vs. 40 %), diarrhoea (28 vs. 19 %; $p=0.033$) and elevations in aminotransferase levels (13 vs. 8 %) reported most commonly [59]. The overall incidence of treatment-related adverse events was significantly higher with gefitinib than with icotinib (70 vs. 61 %; $p=0.046$) [59].

Interstitial lung disease

Gefitinib has been associated with interstitial lung disease (ILD), a rare but potentially fatal adverse event. In the pooled analysis of ISEL, INTEREST and IPASS, 1.3 % of gefitinib recipients had ILD, often of grade 3 or 4 severity [8]. Where reported, <2.5 % of ILD cases were fatal in clinical studies [47, 58, 60, 61, 66–68]. It is recommended that gefitinib treatment should be discontinued in patients with confirmed ILD [8].

A large Japanese pharmacoepidemiological cohort and nested case–control study ($n=3159$) determined the risk factors for ILD in patients receiving gefitinib or chemotherapy for 12 weeks [84]. The study identified smoking, poor World Health Organization PS (score of≥2), reduced (≤50 %) normal lung on computed tomography (CT) scan, recent diagnosis of NSCLC (<6 months), pre-existing ILD, older age (≥55 years old) and concurrent cardiac disease as risk factors for developing ILD, regardless of the treatment they were receiving [8, 84]. The risk of developing ILD was found to be higher with gefitinib than with chemotherapy (adjusted odds ratio (OR) 3.2; 95 % CI 1.9–5.4), particularly during the first 4 weeks of treatment (adjusted OR 3.8; 95 % CI 1.9–7.7); thereafter the relative risk for ILD was somewhat lower (adjusted OR 2.5; 95 % CI 1.1–5.8) [8, 84]. In patients who developed ILD, the mortality rate because of ILD was 31.6 % in gefitinib recipients compared with 27.9 % in chemotherapy recipients, with age≥ 65 years, smoking history, pre-existing ILD, reduced (≤50 %) normal lung on CT scan, and/or extensive (≥50 %) areas adherent to pleura found to be strong predictors of a fatal outcome [84].

The incidence of ILD in the ISEL study appeared to be higher in the Asian population (3 % in gefitinib vs. 4 % in placebo recipients) than in the overall population (1 vs. 1 %) [63]. Among Asians, Japanese patients receiving gefitinib appeared to be particularly at risk, with the rate of ILD in East Asian countries (excluding Japan) being 0.17 % compared with 0.23 % in the rest of the world (excluding Japan), based on data from the 215,000 patients in the Global Drug Safety database [84]. Although the reasons for the higher incidence of ILD in Japan are unclear, it has been suggested that constitutional and environmental factors specific to Japan or Japanese patients may relate to these differences [84].

In chemotherapy-naïve Japanese patients with NSCLC and activating *EGFR* mutations, 5 % (10 of 201) of gefitinib recipients developed ILD, of whom 2.5 % (five patients) had ILD of grade ≥3 severity, and 1 % (two patients) died because of ILD, according to a pooled analysis of the NEJ002 and WJTOG3405 studies [85]. Smoking history was a significant ($p=0.01$) risk factor for ILD, and smokers had a significantly ($p=0.03$) higher incidence rate for ILD than non-smokers during the first 4 weeks of treatment (4.7 vs. 0 %) [85].

Dosage and administration

In the EU, oral gefitinib is indicated for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of *EGFR* tyrosine kinase [8]. In Japan, gefitinib is indicated for the treatment of *EGFR* mutation-positive inoperable or recurrent NSCLC [86]. The recommended dosage of gefitinib is 250 mg administered orally once daily (at about the same time each day), without regard to food [8, 86]. The gefitinib tablet can be swallowed whole or administered as a dispersion in noncarbonated water [8]. Local prescribing information should be consulted for comprehensive information on dosage adjustments, contraindications, warnings and precautions.

Place of gefitinib in the management of locally advanced or metastatic non-small cell lung cancer

Pharmacological treatment options for patients with NSCLC include chemotherapy (e.g. platinum-based regimens) and TKIs (e.g. EGFR TKIs and the dual anaplastic lymphoma kinase and MET TKI, crizotinib), with the choice of therapy determined by factors such as molecular pathology, tumour histology and the PS of the patient [87, 88]. Current European guidelines recommend first-line treatment with EGFR TKIs (gefitinib, erlotinib, afatinib) in patients with advanced or metastatic NSCLC who have activating *EGFR* mutations [87, 88]. EGFR TKIs are also recommended as second- or subsequent-line treatment in patients with activating *EGFR* mutations who have not been treated with an EGFR TKI previously [87, 88]. In the EU, the first-generation agents, gefitinib and erlotinib (reversible TKIs), and the second-generation agent, afatinib (irreversible TKI), are currently approved for use in NSCLC patients with activating *EGFR* mutations.

Gefitinib is a small-molecule EGFR TKI ("Pharmacodynamic Properties") administered orally with or without food; by contrast, erlotinib and afatinib should be taken without food. Gefitinib has demonstrated efficacy in patients with locally advanced or metastatic NSCLC and activating *EGFR* mutations and in patients who were clinically selected (e.g., never-smokers, Asian patients) and more likely to harbour *EGFR* mutations ("Therapeutic Efficacy"). In these patients, gefitinib as first- or subsequent-line treatment significantly prolonged PFS and improved ORRs and/or HR-QOL parameters in large, well designed phase III or IV clinical studies ("Therapeutic Efficacy"). OS did not increase significantly with gefitinib, although post-study treatments may have had a confounding effect on this outcome ("Therapeutic Efficacy"); real-world studies suggest an OS benefit in NSCLC patients in the post-gefitinib era ("Real-World Evidence"). Compared with chemotherapy, gefitinib as first-line therapy was found to be superior to carboplatin plus paclitaxel and cisplatin plus docetaxel and did not differ significantly from gemcitabine plus cisplatin ("In Chemotherapy-Naïve Patients"); as second- or subsequent-line treatment, gefitinib was superior to pemetrexed and at least as effective as docetaxel in terms of these parameters ("In Chemotherapy-Experienced Patients").

Gefitinib was generally well tolerated in these studies, with mild or moderate skin reactions, gastrointestinal disturbances and elevations in liver enzymes occurring most commonly with gefitinib treatment ("Tolerability"). ILD was also reported in gefitinib recipients, with the risk being generally higher in Asian patients (more so in Japanese patients); smoking history was found to be a significant risk factor for this adverse event ("Interstitial Lung Disease"). Compared with chemotherapy, gefitinib was generally associated with fewer haematological adverse events, neurotoxicity, asthenic disorders, as well as grade ≥3 adverse events ("Versus Chemotherapy").

In keeping with the results of these studies, gefitinib is approved for the treatment of *EGFR* mutation-positive locally advanced or metastatic NSCLC (in the EU), or inoperable or recurrent NSCLC (in Japan) ("Dosage and Administration"). Current European guidelines recommend routine *EGFR* somatic mutation testing for all patients with advanced or recurrent NSCLC who have non-squamous tumours and in selected patients with squamous tumours (patients with minimal or remote smoking history), using a well-validated and robust methodology [45]. In clinical studies, *EGFR* mutation status was assessed in tumour tissue by direct gene sequencing (the historical standard [44]) or by using targeted *EGFR* mutation tests (e.g. PNA-LNA PCR clamp and ARMS), which are more sensitive for detecting specific mutations [89]. Although tumour tissue obtained during biopsy or resection is considered the preferred sample type [44, 49], recent evidence suggests that small biopsies, cytology samples and cfDNA from plasma samples could be used as substitutes if sufficient tumour tissue is not available ("Diagnostic Studies"). Currently, tissue biopsy and cytology samples are considered suitable for molecular testing, provided they are handled appropriately [45]; in addition, the European regulatory agency has recently approved the use of cfDNA when a tumour sample is not available. Results from the recently completed non-interventional Europe-Japan diagnostic study for *EGFR* testing (ASSESS) [90] and the ongoing interventional diagnostic Asia-Pacific and Russia diagnostic study for *EGFR* testing (IGNITE) [91] will help to further establish whether cfDNA plasma samples are a suitable and less invasive substitute for tumour tissue [49].

There are limited data directly comparing gefitinib with other EGFR TKIs in patients with locally advanced or metastatic NSCLC. In phase II or III studies, gefitinib did not differ significantly from erlotinib in clinically selected patients and it was noninferior to icotinib (approved for use only in China) in Chinese patients ("Versus Other EGFR TKIs"). The tolerability profile of gefitinib was generally similar to that of erlotinib (phase II study [72]) and icotinib (phase III study [59]), with any-grade skin rash being the most common adverse event with all three agents ("Versus Other EGFR TKIs"); however, the incidence of grade 3 or 4 skin rash appeared to be lower with gefitinib than with erlotinib (phase III study [71]).

In addition to these studies, several retrospective registry studies showed similar efficacy of gefitinib and erlotinib in patients with advanced/metastatic or recurrent NSCLC [92, 93] or stage IIIB or IV pulmonary adenocarcinoma [94]. Furthermore, a recent network meta-analysis indirectly compared the efficacy of gefitinib, erlotinib, icotinib and afatinib and showed that the four agents had generally similar efficacy in patients with NSCLC and activating *EGFR* mutations [95]. In terms of tolerability, results suggested that gefitinib and icotinib may be associated with less severe rash and diarrhoea than with erlotinib or afatinib [95]. However, additional, well-

designed, head-to-head comparisons of gefitinib with other EGFR TKIs are needed to position gefitinib more definitively.

In addition to its use in the approved indication, gefitinib is also being evaluated in other settings, including as neoadjuvant (NCT01833572) or adjuvant (NCT01405079) therapy in patients with early-stage NSCLC with activating *EGFR* mutations. Studies are also investigating optimal treatment following acquired resistance to gefitinib (e.g. IMPRESS and NCT01746277), as most responders to EGFR TKIs, including gefitinib, eventually develop resistance to the drug ("Drug Resistance"). Recently available results from the IMPRESS study in patients with acquired resistance to first-line treatment with gefitinib did not show significant improvement in PFS when continuing gefitinib therapy in addition to chemotherapy (cisplatin plus pemetrexed) relative to chemotherapy alone (abstract presentation) [96]. These results indicate that chemotherapy alone should be used in patients who progress after first-line treatment with EGFR TKIs [96].

In conclusion, current evidence indicates that gefitinib monotherapy is an effective and generally well-tolerated first- or subsequent-line treatment option for patients with NSCLC and activating *EGFR* mutations who have not received an EGFR TKI previously.

Data selection sources Relevant medical literature (including published and unpublished data) on gefitinib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 16 January 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

Search terms Gefitinib, non-small cell lung cancer, NSCLC, *EGFR*-mutation positive, locally advanced, metastatic, first-line, second-line.

Study selection Studies in patients with locally advanced or metastatic non-small cell lung cancer who received gefitinib as first-line or subsequent-line therapy. When available, large, well-designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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