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Gefitinib for the treatment of non-small-cell lung cancer

Lynn Campbell[†], Fiona Blackhall & Nicholas Thatcher
Christie Hospital NHS Foundation Trust, Medical Oncology, Wilmslow Road, Manchester, UK

Importance of the field: The epidermal growth factor receptor (EGFR) is a leading target for treatment of non-small-cell lung cancer (NSCLC). Recent trials of the small-molecule EGFR inhibitor gefitinib have now more clearly defined indications for usage, and clinical and molecular factors predictive of benefit.
Areas covered in this review: A systematic search of the literature (Medline, ASCO, WCLC meeting abstracts) was performed from January 2000 to January 2010. The Phase III INTEREST study found gefitinib in unselected, pretreated patients was not inferior to docetaxel chemotherapy in overall survival, offering improved quality of life and superior toxicity profile. The Phase III IPASS study demonstrated improved progression-free survival with gefitinib compared with paclitaxel–carboplatin chemotherapy in chemotherapy-naive, never/light ex-smokers with adenocarcinoma histology. Stratifying for EGFR mutation revealed mutation-positive patients had superior outcomes with gefitinib compared with chemotherapy. Subsequent studies (WJOG4305, NEJ002), selecting only EGFR mutation-positive patients prospectively confirm this finding.
What the reader will gain: The profile of gefitinib and landmark trials in NSCLC are summarized. How biomarkers may further optimize therapeutic benefit is highlighted.
Take home message: Gefitinib is expected to have an important impact on management of pretreated and selected chemotherapy-naive patients with advanced NSCLC. In addition, activating EGFR mutations are proven to be of value for prediction of those who will derive most benefit.

Keywords: epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, INTEREST, IPASS, molecular targeted therapy, non-small-cell lung cancer

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1. Introduction

Lung cancer is the most common cause of cancer death worldwide, accounting for 1.18 million deaths annually [1]. The majority of cases present at an advanced, metastatic stage and are non-small-cell lung cancers (NSCLC), for which platinum-based combination chemotherapy is standard of care for patients of good performance status [2]. Various platinum-based regimens have achieved similar results with median overall survival in the order of 8 – 10 months, and 1-year survival about 30 – 40% [3-5]. Recently, an additional survival advantage for pemetrexed–cisplatin chemotherapy in non-squamous NSCLC was demonstrated, highlighting the importance of histological subtyping [6].

With knowledge of the molecular pathways promoting tumour cell growth and survival, new targeted agents have been developed. The epidermal growth factor receptor (EGFR), and its associated tyrosine kinase signalling pathways have emerged as a leading target for NSCLC therapy. EGFR overexpression, observed in many solid tumours including NSCLC, has been correlated with poor prognosis,

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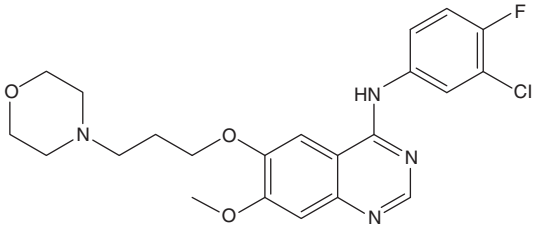
Box 1. Drug summary.

Drug name (generic)	Gefitinib, Iressa
Phase	Phase III/postmarketing
Indication	Advanced or metastatic NSCLC (stage IIIb/IV), selected EGFR-mutation-positive patients across all lines of therapy in Europe Widely used in advanced NSCLC in the pretreated setting in Japan and Asia
Pharmacology	Orally bioavailable, competitive, reversible EGFR-TKI, suitable for once-daily dosing. Linear dose-dependent pharmacokinetics. Metabolized by the liver and excreted via faeces
Route of administration	Oral
Chemical structure	
Pivotal trials	1) The ISEL study compared gefitinib with placebo in heavily pretreated patients with advanced NSCLC; failed to demonstrate an overall survival benefit for gefitinib in an unselected population 2) The Phase III INTEREST study – Overall survival with gefitinib in unselected, pretreated patients, was not inferior to docetaxel; improved quality of life, superior toxicity profile with gefitinib therapy 3) The Phase III IPASS trial – Improved progression-free survival (PFS) with gefitinib compared with paclitaxel-carboplatin chemotherapy in chemotherapy-naive, never- or light smokers with adenocarcinoma histology. In subset of EGFR-mutation-positive patients, PFS was significantly prolonged with gefitinib compared with chemotherapy 4) The NEJ002 and WJTOG3405 Phase III studies in Japanese populations support the IPASS results, demonstrating superior response rate and significant improvement in PFS compared with paclitaxel-carboplatin and docetaxel-cisplatin respectively, in chemotherapy-naive, EGFR-mutation-positive patients with advanced or recurrent NSCLC postsurgery

decreased survival and increased metastatic potential [7-11]. Small-molecule tyrosine kinase inhibitors (TKIs) of EGFR have now demonstrated efficacy in various clinical settings. This article summarizes the evolving role of gefitinib (**Box 1**) as the first clinically available EGFR-TKI in the management of NSCLC, and the relevance of biomarkers, such as EGFR mutation and gene copy number in determining therapeutic benefit.

2. Treatment overview

A therapeutic plateau has been reached with conventional chemotherapy for advanced NSCLC with the sole exception of pemetrexed–cisplatin in non-squamous cancers. Inhibiting EGFR activity using monoclonal antibodies, which block ligand binding to the extracellular domain of EGFR, or small-molecule TKIs, which competitively inhibit ATP binding at the intracellular catalytic domain of EGFR, has provided new therapeutic options. These strategies seem to be equally effective in blocking downstream receptor-dependent signalling pathways *in vitro*. The monoclonal antibody cetuximab (Erbitux®, Bristol-Myers Squibb, UK) is at present approved for use in advanced colorectal and head and neck cancers [12-14]. In combination with cisplatin–vinorelbine chemotherapy in the FLEX (first-line treatment for patients with EGFR-expressing advanced NSCLC) Phase III trial, cetuximab demonstrated superior response rates (36.6 vs 29%) and median overall survival (11.3 vs 10.1 months; HR = 0.871, 95% CI 0.762 – 0.996, p = 0.044) [15]. The European Medicines Agency (EMEA), however, has not extended cetuximab's license to cover NSCLC.

Erlotinib (Tarceva®, OSI Pharmaceuticals, NY, USA), a second EGFR-TKI, has been extensively investigated in NSCLC. Similar to gefitinib, it exhibits potent inhibition of EGFR phosphorylation, with IC_{50} doses in the nanomolar range *in vitro*. Erlotinib is approved at present for the treatment of advanced or metastatic NSCLC following the failure of one or two previous chemotherapies. The BR21 registration trial for the FDA in November 2004 demonstrated improved survival compared with placebo in patients with pretreated NSCLC [16]. It is anticipated that new dual or irreversible TKIs now under investigation will show additional benefit in NSCLC. Such agents include the irreversible EGFR-TKIs, BIBW 2992 (Boehringer Ingelheim, Berkshire, UK) and CL-387785 (Calbiochem, CA, USA), combined EGFR/HER-TKIs, HKI-272 (Neratinib, Wyeth, Maidenhead, UK), HKI-357 (Wyeth), and pan-HER inhibitors, EKB-569 (Wyeth) and CI-1033 (Pfizer, MI, USA).

The vascular endothelial growth factor (VEGF) signalling pathway has also been targeted, since the growth of most solid tumours is angiogenesis dependent. Bevacizumab (Avastin®, Genentech & Roche), a VEGF-receptor (VEGFR) inhibitor, is available. A pivotal trial in advanced NSCLC combining paclitaxel–carboplatin and bevacizumab improved objective response rates (35 vs 15%, $p < 0.001$), progression-free survival (PFS; 6.2 vs 4.5 months, $p < 0.001$) and median overall survival (12.3 vs 10.3 months; HR = 0.79, 95% CI 0.67 – 0.92, $p = 0.003$) compared with chemotherapy alone in patients of good performance status with non-squamous histology [17]. The later AVAIL (avastin in lung) trial combined gemcitabine–cisplatin chemotherapy with bevacizumab or placebo, with maintenance bevacizumab or placebo continued until disease progression. Although PFS was improved, this trial failed to demonstrate improvement in overall survival [18,19].

3. Gefitinib: structure and mechanism of action

Gefitinib (4-Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy], ZD1839, Iressa™ Astra Zeneca, Inc., London, UK) is a synthetic, orally available, low-molecular-weight (447 kDa) anilinoquinazoline, with the molecular formula $C_{22}H_{24}ClFN_4O_3$ Gefitinib selectively inhibits intracellular tyrosine kinase activity of the EGFR by binding competitively at the highly conserved ATP site of the tyrosine kinase region, inhibiting phosphorylation of EGFR and downstream signal transduction pathways.

4. Pharmacodynamic properties

NSCLC cell line and xenograft data found that gefitinib dose-dependently inhibited cell proliferation and tumour growth and potentiated the cytotoxic effects of chemotherapy or radiation, independent of EGFR expression levels [20,21]. Efficacy in chemotherapy-resistant NSCLC models was also demonstrated.

In Phase I studies of continuous daily gefitinib dosing, the maximum tolerated doses (MTDs) were 800 and 1000 mg/day ; however, demonstrable anti-tumour activity and biological effects were apparent at much lower doses [22-25]. Analysis of pharmacodynamic markers in normal skin before and after 28 days' treatment indicated inhibition of EGFR phosphorylation and downstream signalling pathways at doses as low as 150 mg/day [22,26]. In the Phase II IDEAL studies, tumour EGFR levels did not correlate with gefitinib response [27]. Pharmacodynamic studies indicate gefitinib's anti-tumour effects result from blockade-induced upregulation/accumulation of the cyclin-dependent kinase inhibitors, $p27^{kip1}$ or $p21^{cip1/waf1}$ and retinoblastoma protein in its underphosphorylated form, resulting in G1 phase cell cycle arrest [28,29]. Simultaneous downregulation of growth factors including VEGFR, basic fibroblast growth factor (bFGF) and transforming growth factor-alpha (TGF-α) have also been observed [30].

5. Pharmacokinetic properties and metabolism

Single-dose gefitinib pharmacokinetic studies were done in both healthy volunteers and patients with solid tumours. Gefitinib was relatively slowly absorbed, with peak plasma concentrations (C_{max}) occurring 3 – 7 h after administration [31,32]. Oral bioavailability was similar in both healthy volunteers and cancer patients and not significantly altered by the presence of food [32]. Linear dose-dependent kinetics were demonstrated, with increases in AUC and C_{max} correlating with increasing drug concentration, up to 700 mg [24,25]. Significant interindividual variability in AUC and C_{max} was observed, with up to 15-fold differences between individuals [32]. Steady-state plasma concentrations were achieved within 10 days of dosing, with gefitinib extensively distributed throughout the body (mean steady state volume of distribution of 1400 litres) following intravenous administration in cancer patients. Gefitinib was preferentially concentrated in tumour tissue in xenograft models at levels above that required to achieve complete inhibition of EGFR phosphorylation [33]. Similarly, in both NSCLC and breast cancer patients, tumour penetration of gefitinib was consistently higher than corresponding plasma concentrations [33,34].

Gefitinib undergoes extensive hepatic metabolism, predominantly by expressed cytochrome P450 isozyme 3A4 (CYP3A4) and, to a much lesser extent, CYP3A5 and CYP2D6 [35,36]. Five metabolites have been identified in human faeces. Of these, O Desmethyl gefitinib (M523595) is the major metabolite which has exposure comparable to gefitinib [37]. As CYP3A4 is variably expressed in the human liver this may account for interindividual variability in pharmacokinetics.

In healthy male volunteers, co-administration of the CYP3A4 inducer rifampicin significantly reduced AUC by 83%, whereas the inhibitor itraconazole increased AUC by 78%, thus increasing gefitinib exposure [38]. No apparent change in the safety profile of gefitinib as a result of drug co-administration was observed and therefore dose adjustment is not generally recommended.

Gefitinib total plasma clearance was rapid, with a mean elimination half-life ($t_{1/2}$) of $\leq$ 48 h [25,26]. Excretion was predominantly via faeces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

6. Clinical efficacy

6.1 Phase I

An initial healthy volunteer study established tolerability of single oral dosing (50 – 500 mg) and daily dosing for 14 days (100 mg/day) [31]. Four open-label, Phase I, dose-escalation trials determined gefitinib's safety profile in a variety of solid tumours [23-25,39]. Two studies recruited 95 patients to receive intermittent gefitinib treatment (14 days treatment, followed by 14 days without treatment),

over eight dose levels ranging from 50 to 925 mg daily [24,25]. The MTD occurred at 700 mg/day in both studies, with the development of grade 3 diarrhoea or elevated liver transaminases. Grade 1/2 acneform rash and diarrhoea were reported frequently, and were commoner at higher doses. Though not the primary trial end point, objective partial responses in patients with advanced NSCLC were observed in 9 of 39 patients in these studies [24,25]. Additional studies evaluated gefitinib treatment daily (150 – 1000 mg/day) over a continuous 28-day cycle, until disease progression or toxicity [22,23]. The MTDs were 800 and 1000 mg/day respectively. Similar manageable toxicity was reported, and pharmacodynamic studies over this dose range found effective inhibition of the biological target, EGFR, in serial skin biopsies [22,23].

6.2 Phase II

The IDEAL-1 and -2 trials independently established the tolerability of gefitinib monotherapy in patients with refractory or relapsed advanced NSCLC [40,41]. IDEAL-1 recruited 210 patients in Australia, Europe, South Africa and Japan who had received one or two previous lines of chemotherapy including a platinum agent, whereas the IDEAL-2 protocol required US patients to have received two or more chemotherapy regimens, including both a platinum agent and docetaxel. Patients were predominantly performance status 0 and 1; however, each study included poor-performance patients (12.9 and 19.6%, respectively). Both trials randomized patients to receive either gefitinib 250 or 500 mg/day . Objective response rates were similar in both arms in IDEAL-1 (18.4 and 19.0%), and IDEAL-2 (11.8 and 8.8%). Median overall survival was 7.6 months in IDEAL-1 and 7.0 months in IDEAL-2, at the 250-mg dose. Cancer-related symptoms improved in approximately 40% of patients receiving the 250-mg dose in both studies. Relief of symptoms was generally rapid, sustained and correlated with the clinical benefits of tumour response and prolonged PFS. This was an important trial end point particularly in IDEAL-2 as all patients enrolled were symptomatic on entry. Most adverse events were mild (grade 1/2), but were more severe at the higher gefitinib dose in both studies. These trials indicated no difference in efficacy between 250 mg and 500 mg of gefitinib, but less toxicity at the lower dose.

The efficacy and tolerability of gefitinib in previously untreated patients has also been investigated. The Phase II IRESSA in NSCLC versus the INVITE (vinorelbine investigation in the elderly) study compared gefitinib 250 mg/day and vinorelbine (30 mg/m^2 on days 1 and 8 every 21 days) in elderly patients (≥ 70 years) with advanced NSCLC [42]. Patients (n = 196) with performance status 0 – 2 were randomized. Gefitinib was administered until disease progression or intolerance; vinorelbine was prescribed for up to six cycles. Low overall response rates of 3.1 and 5.1% for both agents were reported. Overall quality of life improvement rates (FACT-L) were higher with gefitinib (24.3 vs 10.9%), while symptom improvement rates were similar for the two regimens (36.6 vs 31%). Tolerability was significantly better with gefitinib, with fewer treatment-related grade 3 – 5 adverse events (12.8 vs 41.7%). No significant difference in survival was demonstrated. Interestingly, by stratifying patients according to EGFR gene copy number, EGFR positivity resulted in improved overall survival with vinorelbine treatment. The IRESSA NSCLC Trial Evaluating Poor Performance Patients (INSTEP) trial (n = 201), reported a 6% response rate to gefitinib and a non-significant trend towards improved efficacy end points in poor-performance patients (performance status 2,3, unfit for chemotherapy) with advanced-stage NSCLC, compared with best supportive care [43].

More recently, biomarkers for gefitinib response have been used to select patients for EGFR-TKI therapy. A number of Phase II studies, conducted in selected EGFR-mutation-positive populations have reported encouraging response rates and prolonged PFS times (**Table 1**). These are discussed further in the context of biomarker development (section 6.5).

6.3 Phase III – efficacy of gefitinib in pretreated NSCLC

The ISEL (IRESSA survival evaluation in lung cancer) study compared gefitinib monotherapy with placebo in 1692 patients with advanced NSCLC, who had received one or two previous chemotherapy regimens [44]. Gefitinib failed the primary analysis of significantly prolonged survival compared with placebo in this setting (median overall survival 5.6 vs 5.1 months; HR = 0.89, 95% CI 0.77 – 1.02, p = 0.087). This is in contrast to the survival advantage reported with erlotinib in advanced NSCLC by the BR21 trial (HR = 0.7, 95% CI 0.58 – 0.85, p < 0.001, median overall survival 6.7 vs 4.7 months) [16]. It is noteworthy that in the ISEL study 90% of patients were refractory to their last treatment (defined as recurrence or progression of disease within 90 days of the last dose of treatment). This was not necessary for inclusion in the BR21 study and may explain in part the differing outcomes observed in these two studies. In a prospectively planned subgroup analysis, gefitinib treatment did, however, prolong median overall survival in never-smokers (8.9 vs 6.1 months; HR = 0.67; 95% CI 0.49 – 0.92, p = 0.012) and the Asian population (9.5 vs 5.5 months; HR = 0.66; 95% CI 0.48 – 0.91, p = 0.01), factors typically associated with the presence of an EGFR mutation.

The INTEREST (IRESSA NSCLC trial evaluating response and survival against taxotere) trial reported survival following gefitinib therapy was not inferior to docetaxel chemotherapy in advanced, pretreated NSCLC (median overall survival 7.6 vs 8.0 months; HR = 1.020, 96% CI 0.905 – 1.150) [45]. The study recruited 1466 patients from 24 countries with refractory or relapsed advanced NSCLC. All had received previous platinum-containing chemotherapy and were randomized to receive either gefitinib 250 mg/day or thrice-weekly docetaxel 75 mg/m^2. Median survival was consistent with previously reported studies of docetaxel in this setting [46,47]; however, important improvements in quality of life in favour of gefitinib were demonstrated (FACT-L: OR = 1.99, 95% CI

Table 1. Summary of prospective studies of gefitinib in EGFR-mutation-positive NSCLC patients.

Study	No. of patients with EGFR mutation	Ethnicity	Overall DCR rate (%)	Complete response	Partial response	Median PFS (months)
Yoshida *et al.* [91]	21	Japanese	91	3 (14%)	16 (76%)	7.7
Sunaga *et al.* [92]	21	Japanese	90	3 (14%)	13 (62%)	12.9
Inoue *et al.* [93]	16	Japanese	88	0 (0%)	12 (75%)	9.7
Asahina *et al.* [94]	16	Japanese	81	2 (13%)	10 (62%)	8.9
Sugio *et al.* [95]	19	Japanese	89.5	0 (0%)	12 (63.2%)	7.1
Tamura *et al.* [96]	28	Japanese	96	1 (3.6%)	20 (71.4%)	11.5
van Zandwijk *et al.* [97]	13	Caucasian	92	1 (8%)	10 (77%)	14
Sequist *et al.* [89]	31	Asian & others	94	1 (3%)	16 (52%)	9.2
Inoue *et al.* [88]	30	Japanese	90	1 (3%)	18 (62%)	6.5
Sutani *et al.* [90]	27	Japanese	NR	1 (3.7%)	20 (74%)	9.4

DCR: Disease control rate; EGFR: EGF receptor; NR: Not recorded; PFS: Progression-free survival.

1.42 – 2.79, p < 0.0001). Lung cancer symptom improvement rate was similar in each arm (20.4 vs 16.8%; OR = 1.29; 95% CI 0.93 – 1.79; p = 0.1329); however, gefitinib was associated with better tolerability (treatment-related grade 3/4: 8.5 vs 40.7%).

In a pre-planned subgroup analysis, predictors of gefitinib efficacy identified from earlier placebo trials (including never smoking, female, Asian origin and adenocarcinoma histology), were associated with favourable overall survival in both the gefitinib and docetaxel treatment arms, indicating that these factors may generally predict for better outcome, independent of treatment received. A panel of biomarkers, including EGFR expression determined by immunohistochemistry (IHC), EGFR copy number and EGFR or kras mutations were not found to predict for a differential overall survival between gefitinib and docetaxel [48].

The V-15-32 trial, a much smaller study (n = 489) comparing gefitinib and docetaxel (60 mg/m^2) in a similar patient population was conducted in Japan [49]. Objective responses following gefitinib therapy were almost double that observed with chemotherapy (22.5 vs 12.8%, p = 0.009). No statistically significant difference in overall survival and PFS between the treatment arms (overall survival: p = 0.33; PFS: p = 0.34) was observed. However, the primary objective of non-inferior survival for gefitinib was not met (HR = 1.12; 95.24% CI 0.89 – 1.40, non-inferiority criterion: < 1.25). The fact that non-inferiority in survival was met in INTEREST, but not in V-15-32, may be attributable to smaller patient numbers and imbalances in post-study crossover treatment in the V-15-32 study (36% of gefitinib arm vs 56% of docetaxel arm crossed over).

Additional Phase II and III study data largely support the findings of the INTEREST study. The Phase II, multi-centre, randomized trial of gefitinib or docetaxel as second-line therapy (SIGN) enrolled 141 patients and reported similar efficacy in symptom improvement, the primary end point, in both arms (33.8% for gefitinib, 26.0% for docetaxel) [50]. Objective response rates and median overall survival were 13.2 and 13.7%, and 7.5 and 7.1 months for gefitinib and docetaxel respectively. Similarly, the ISTANA (IRESSA as second-line therapy in advanced NCSLC) Phase III trial (n = 161), compared gefitinib with docetaxel in a Korean population [51]. Superior response rates (28.1 vs 7.6%, p = 0.0007) and PFS (HR = 0.729, 90% CI 0.533 – 0.9984, p = 0.04) in response to gefitinib therapy were reported. Overall survival, however, was not significantly prolonged by gefitinib compared with docetaxel (HR = 0.87, 95% CI 0.613 – 1.236, p = 0.437).

Taken together, these studies indicate that gefitinib is better tolerated, is associated with enhanced quality of life and may be as beneficial in terms of survival as docetaxel in advanced, pretreated NSCLC.

6.4 Phase III – efficacy of gefitinib in chemotherapy-naive patients

The large Phase III INTACT-1 and INTACT-2 trials both recruited chemotherapy-naive patients with stage III/IV NSCLC [52,53]. Up to six cycles of platinum-based chemotherapy were administered (gemcitabine-cisplatin or carboplatin-paclitaxel, respectively), with patients randomized to receive gefitinib 250 mg daily, 500 mg daily or placebo, concurrently. Gefitinib or placebo was continued until disease progression. No survival benefit was demonstrated in either study and toxicity was greater with the 500-mg dose of gefitinib than the lower dose or placebo, in keeping with the findings of the IDEAL studies. Concomitant drug scheduling may have contributed to the lack of efficacy, with the cytostatic effects of gefitinib (halting cells in the G1 phase of the cell cycle), potentially reducing chemotherapy effectiveness. In both INTACT trials the time to progression (TTP) survival curves indicated that, after 5 – 6 months of treatment, the gefitinib arms had a trend towards better TTP. In addition, in an exploratory subset analysis, patients with adenocarcinoma receiving more than 90 days of chemotherapy in the INTACT-2 study had a trend towards prolonged survival,

suggesting a possible gefitinib maintenance effect. These findings indicate that EGFR-TK inhibition may be more effective if given sequentially. A number of studies have demonstrated feasibility of EGFR-TKI treatment following primary chemotherapy or chemoradiation in Phase II [54,55]. The SWOGS0023 Phase III study assessed the role of gefitinib maintenance in untreated, stage III NSCLC. Patients received concurrent chemoradiation (cisplatin, etoposide, concurrent radiation 1.8 – 2 Gy, total 61 Gy) and consolidation docetaxel chemotherapy, and if non-progression of disease, patients were randomized to gefitinib or placebo [56]. The study was closed early after an unplanned interim analysis following the ISEL trial result, with just 243 patients enrolled on the maintenance arm. No survival advantage from randomization was demonstrated in the gefitinib arm compared with placebo (median overall survival 23 vs 35 months, HR = 0.633, 95% CI 0.44 – 0.91, p = 0.013), in keeping with preliminary data from an earlier trial of chemoradiation, followed by gefitinib maintenance [57]. Similarly, the role of adjuvant gefitinib postoperatively has been assessed [58]. Patients (n = 38) with completely resected stage I – IIIA disease were randomized to gefitinib 250 mg daily or placebo for up to 2 years. Owing to safety concerns, the study was closed prematurely; however, no unexpected adverse events were recorded.

More promising results have been achieved in stage IIIb/IV disease, treated with chemotherapy and sequential EGFR-TKI therapy. The Japanese WJTOG0203 Phase III study (n = 604) assessed gefitinib maintenance therapy on completion of a primary platinum doublet chemotherapy for advanced NSCLC [59]. Patients were randomized before chemotherapy, rather than on completion. Six cycles of standard chemotherapy was compared with three cycles of chemotherapy followed by gefitinib. Progression-free survival was significantly improved in favour of gefitinib maintenance (HR = 0.68, 95% CI 0.57 – 0.8, p < 0.001). Overall survival was not significantly prolonged (HR = 0.86, 95% CI 0.72 – 1.03, p = 0.11); however, in a pre-planned subset analysis, adenocarcinoma histology was correlated with superior overall survival on gefitinib maintenance compared with the chemotherapy arm (n = 467, HR = 0.79, CI 0.65 – 0.98, p = 0.03). Additional large studies are required, however, to define this role clearly in stage III/IV NSCLC.

The IRESSA Pan-Asia study (IPASS) was the first trial to investigate the role of gefitinib monotherapy in a highly selected NSCLC patient population, compared with standard platinum doublet chemotherapy [60]. This Phase III study enrolled 1217 chemotherapy-naive patients from East Asia. To meet entry criteria, patients had confirmed advanced stage lung adenocarcinomas and a previous light (stopped smoking for ≥ 15 years and had a total of ≤ 10 pack-years of smoking) or non-smoking (< 100 cigarettes in their lifetime) history. Patients received either gefitinib 250 mg/day or up to six cycles of carboplatin–paclitaxel chemotherapy. The primary end point of demonstrating non-inferiority in PFS was met and exceeded, with gefitinib achieving superior PFS compared with chemotherapy (HR = 0.74, 95% CI 0.65 – 0.85, p < 0.001). To investigate the relevance of EGFR mutation in sensitivity to treatment in the IPASS study, 56.1% of patient samples were made available for biomarker analysis. EGFR mutational status was evaluable for 437 of these samples (35.9% of overall population). Patients harbouring an EGFR mutation (n = 261) had a response rate of 71.1% and prolonged PFS if treated with gefitinib compared with chemotherapy (HR for progression or death = 0.48, 95% CI 0.36 – 0.64, p < 0.001). Conversely, in the EGFR wild-type group, PFS favoured chemotherapy treatment (HR for progression or death with gefitinib = 2.85, 95% CI 2.05 – 3.98, p < 0.001). Overall survival data are not yet mature; however, preliminary results indicate similar survival for gefitinib and chemotherapy (HR = 0.91, 95% CI 0.76 – 1.10; median overall survival 18.6 vs 17.3 months; 37% maturity). Gefitinib therapy was again associated with significantly greater increases in quality of life and equivalent symptom improvement compared with chemotherapy. This study therefore suggests a possible role for gefitinib as first-line treatment for patients with EGFR-mutation-positive advanced NSCLC. The smaller, First-SIGNAL, WJTOG3405 and NEJGSG trials support the IPASS data [61-63]. The Korean First-SIGNAL, Phase III study randomized 309 chemotherapy-naive patients with stage IIIB/IV disease to either gefitinib or gemcitabine–cisplatin chemotherapy [63]. Again, all patients were never-smokers with adenocarcinoma histology. The primary objective of improved overall survival was not met. Objective response rates and PFS favoured the gefitinib arm, but did not reach statistical significance (RR = 53.5 vs 46.3%, p = 0.1533, 1 year PFS: 20.3 vs 5.0%). When stratified for EGFR mutational status, mutation positive patients receiving gefitinib (n = 26), compared with EGFR wild-type patients (n = 27), had a significantly improved response rate (84.6 vs 25.9%) and prolonged median PFS (8.4 vs 2.1 months; HR = 0.394, p = 0.0006). No such differences were found in the chemotherapy arm.

The WJTOG 3405 Phase III study accrued only chemotherapy-naive, EGFR-mutation-positive patients with recurrent disease post-resection or stage IIIb/IV NSCLC [61]. The 177 patients received either gefitinib or cisplatin–docetaxel. A significant improvement in PFS, the primary end point and overall response rate (ORR), in favour of gefitinib was demonstrated (ORR = 62.1 vs 32.2%, p < 0.0001, median PFS: 9.2 vs 6.3 months, HR = 0.489, 95% CI 0.336 – 0.71, p < 0.0001). The Phase III, multi-centre NEJGSG study similarly recruited untreated metastatic NSCLC patients with EGFR mutations. The efficacy of gefitinib was compared with paclitaxel–carboplatin chemotherapy and again was associated with superior ORRs (74.4 vs 29%, p < 0.001) and significantly prolonged PFS (HR = 0.357, CI 0.25 – 0.51, p < 0.001) [62]. Follow-up of these study cohorts is ongoing to determine overall survival. All the above Phase III studies are summarized in **Table 2**.

Table 2. Summary of Phase III trial data for gefitinib in patients with advanced NSCLC.

Trial	Treatment arms	No. of patients	Object RR (%)	Median PFS (months)	Median survival (months)	Details
Gefitinib compared with best supportive care in pretreated, advanced NSCLC						
ISEL [44]	Gefitinib 250 mg vs	1129	8.0 (p < 0.0001)	*3.0 (p = 0.0006)	5.6 (HR = 0.89, 95% CI 0.77 – 1.02, p = 0.09)	Included a population highly refractory to treatment Survival advantage in non-smokers and Asians *NB Time to treatment failure assessed rather than PFS
	Placebo	563	1.3%	2.6	5.1	
Gefitinib compared with standard chemotherapy in pretreated, advanced NSCLC						
INTEREST [45]	Gefitinib 250 mg vs	733	9.1 (p = 0.33)	2.2 (p = 0.47)	7.6 (HR = 1.020, 96% CI 0.905 – 0.15)	Gefitinib equivalent to docetaxel in OS, across all patient groups
	Docetaxel 75 mg/m^2	733	7.6	2.7	8	
V-15 – 32 [49]	Gefitinib 250 mg vs	245	22.5 (p = 0.009)	2.0 (p = 0.34)	11.5 (p = 0.33)	Variable numbers crossing over on progression in each arm. Failed to demonstrate gefitinib is non-inferior to docetaxel in OS (HR1.12, 95.24%CI:0.89 – 1.4, non-inferiority criterion < 1.25)
	Docetaxel 60 mg/m^2	244	12.8	2.0	14.0	
ISTANA [51]	Gefitinib 250 mg vs	82	28.1 (p = 0.0007)	3.3 (HR = 0.729, 90% CI 0.53 – 0.998, p = 0.04)	14.1 (p = 0.437)	Second- line therapy in Korean population. Primary end point of PFS significantly favoured gefitinib
	Docetaxel 75 mg/m^2	79	7.6	3.4	12.2	PFS favoured gefitinib.
Gefitinib compared with standard chemotherapy as first-line treatment for advanced NSCLC						
IPASS [60]	Gefitinib 250 mg vs	609	43.0 (p = 0.001)	5.7 (HR: 0.74, 95% CI 0.65 – 0.85, p < 0.001)	18.6	Selected treatment-naïve, Asian patient population (adenocarcinoma, non-smokers). PFS favoured chemotherapy for first 6 months, then gefitinib, potentially due to EGFR mutational status
	Paclitaxel/carboplatin	608	32.2	5.8	17.3	OS data is from preliminary analysis, with only 37% maturity.
Subgroups						
Mutation positive	Gefitinib			9.5		
	Chemotherapy			6.3		
Mutation negative	Gefitinib			1.5		
	Chemotherapy			5.5		

EGFR: EGF receptor; INTACT: Iressa NSCLC trial assessing combination treatment; INTEREST: Iressa NSCLC trial evaluating response and survival against taxotere; IPASS: Iressa Pan-Asia study; ISEL: Iressa survival evaluation in lung cancer; ISTANA: Iressa as second-line therapy in advanced NSCLC; NA: not applicable; NEJGSG: North-East Japan Gefitinib Study group; NSCLC: Non small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; SWOG: South West Oncology Group.

Table 2. Summary of Phase III trial data for gefitinib in patients with advanced NSCLC (continued).

Trial	Treatment arms	No. of patients	Object RR (%)	Median PFS (months)	Median survival (months)	Details
First Signal [63]	Gefitinib vs	159	53.5 (p = 0.1533)	6.1 (HR = 0.813, 95% CI 0.641 – 1.031, p = 0.044)	21.3	Selected treatment-naïve, Asian patient population (adenocarcinoma, non-smokers)
	Gemcitabine/cisplatin	150	46.3	6.6	23.3	When EGFR mutant population selected, significant improvement in RR and PFS in favour of gefitinib (HR: 0.613, 95% CI: 0.308 – 1.22, p = 0.084)
WJTOG 3405 [61]	Gefitinib vs	88	62.1	9.2 (HR = 0.48, 95% CI 0.336 – 0.71, p < 0.0001)	NA	Selected, Japanese, chemo-naïve patients, stage IIIB/IV disease or recurrence postsurgical resection
	Cisplatin/docetaxel	89	32.2	6.3	NA	All EGFR-mutation-positive
NEJ002 [62]	Gefitinib vs	80	74.5	10.3 (HR = 0.357, 95% CI 0.25 – 0.51, p < 0.001)	NA	Selected, Japanese, chemo-naïve patients, stage IIIB/IV disease
	Carboplatin/paclitaxel	75	29	5.3	NA	All EGFR-mutation-positive
Gefitinib in combination with chemotherapy as first-line treatment of advanced NSCLC						
INTACT-1 [53]	Gemcitabine/cisplatin + gefitinib 250 mg	365	51.2	5.8	9.9	
	Gemcitabine/cisplatin + gefitinib 500 mg	365	50.3 (NS)	5.5 (p = 0.76)	9.9 (p = 0.46)	
	Gemcitabine/cisplatin + placebo	363	47.2	6.0	10.9	
INTACT-2 [52]	Paclitaxel/carboplatin + gefitinib 250 mg	345	30.4	5.3	9.8	
	Paclitaxel/carboplatin + gefitinib 500 mg	347	30.0	4.6 (p = 0.06)	8.7 (p = 0.64)	
	Paclitaxel/carboplatin + placebo	345	28.7	5	9.9	

EGFR: EGF receptor; INTACT: Iressa NSCLC trial assessing combination treatment; INTEREST: Iressa NSCLC trial evaluating response and survival against taxotere; IPASS: Iressa Pan-Asia study; ISEL: Iressa survival evaluation in lung cancer; ISTANA: Iressa as second-line therapy in advanced NSCLC; NA: not applicable; NEJGSG: North-East Japan Gefitinib Study group; NSCLC: Non small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; SWOG: South West Oncology Group.

Table 2. Summary of Phase III trial data for gefitinib in patients with advanced NSCLC (continued).

Trial	Treatment arms	No. of patients	Object RR (%)	Median PFS (months)	Median survival (months)	Details
SWOG0023 [56]	Gefitinib 250 mg	118	NA	8.3 (p = 0.17)	23 (HR = 0.633, 95% CI 0.44 – 0.91, p = 0.01)	Phase III trial of maintenance gefitinib, following chemoradiation and consolidation docetaxel in stage III NSCLC.
	Placebo	125		11.7	35	The study was closed early following an unplanned interim analysis
WJTOG0203 [59]	Chemotherapy + gefitinib 250 mg	300	34.2	4.6 (HR = 0.68, 95% CI 0.57 – 0.8, p < 0.001)	13.7 (HR = 0.86, 95% CI 0.72 – 1.03, p = 0.11)	Phase III trial of sequential gefitinib following chemotherapy in stage IIIb/IV NSCLC
	Chemotherapy alone	298	29.3	4.3	12.9	Superior OS in gefitinib arm in adenocarcinomas

EGFR: EGF receptor; INTACT: Iressa NSCLC trial assessing combination treatment; INTEREST: Iressa NSCLC trial evaluating response and survival against taxotere; IPASS: Iressa Pan-Asia study; ISEL: Iressa survival evaluation in lung cancer; ISTANA: Iressa as second-line therapy in advanced NSCLC; NA: not applicable; NEJGSG: North-East Japan Gefitinib Study group; NSCLC: Non small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; SWOG: South West Oncology Group.

6.5 Biomarker development

The reported objective response rate to gefitinib in unselected patients with advanced NSCLC is about 10%, indicating potential to define a biologically identifiable subset of responder patients. Several trials documented a higher probability of responding to EGFR-TKIs for female gender, never-smoking, Asian ethnicity and adenocarcinoma histology [64-66]. These clinical and pathological factors are also associated with the presence of EGFR mutations [67,68].

Several studies have failed to show any relationship between immunohistochemical protein expression and clinical activity [27,69]. High EGFR gene copy number (amplification/high polysomy), found in approximately 30% of patients with NSCLC, has been shown to correlate with significant survival benefit from EGFR-TKI therapy in Phase III clinical trials versus placebo [16,44], but did not predict for a differential survival benefit in active comparator studies [42,69].

Somatic mutations in the tyrosine kinase domain of EGFR have been detected in 30 – 40% of Asian patients but only in approximately 10 – 15% of caucasians. The commonest mutations include a small in-frame deletion in exon 19 (746 – 753, ELREA) and the substitution of leucine for arginine at amino acid 858 in exon 21 (L858R). These mutations enhance kinase activity of EGFR and downstream signalling and may have a critical role in predicting the clinical activity of TKIs [70-73]. The ISEL study reported an objective response rate of 37.5% in 16 EGFR-mutation-positive patients receiving gefitinib, patients with EGFR wild-type disease (n = 116), showed response in only 2.6% cases. A number of Phase II studies, including only EGFR mutant NSCLC patients have demonstrated high objective response rates and disease control in more than 80% of patients (**Table 1**). Moreover, PFS was significantly longer compared with standard platinum doublet chemotherapy. The publication of the IPASS trial was pivotal in demonstrating that EGFR mutational status may be a robust biomarker with which to select patients for treatment with gefitinib [60]. Additional trials have now prospectively assessed this in East Asian populations [61,62].

Treatment failure, despite an initial response to EGFR-TKI therapy commonly occurs. This is thought to be predominantly due to acquired, secondary mutations in EGFR, though this is an area poorly understood at present. Substitution of threoinine at codon 790 by methionine (T790 M) has been identified. Tumours with T790 M have been found to be resistant to reversible TKIs, but remain sensitive to the irreversible inhibitors, such as HKI-272 or CL-387 [74,75]. Amplification of the met gene has also been associated with acquired TKI resistance. Several case reports [76,77], and now prospective Phase II studies, suggest switching EGFR-TKI upon development of resistance may be beneficial in selected patients [78-80].

KRAS mutations, found in up to one-third of human malignancies (reviewed in [81]) are predominantly found in codon 12 or 13 in lung adenocarcinomas [82]. These mutations have been investigated as negative predictors of benefit from EGFR-TKI treatment, but randomized Phase III trials have not found any statistical relevance [69,83].

7. Postmarketing surveillance

With the reporting of no statistically significant survival advantage for gefitinib compared with BSC in refractory, advanced or metastatic NSCLC in the ISEL study in 2005 [44], the FDA restricted labelling of gefitinib. In Europe now, with favourable data from the recent INTEREST and IPASS trials, gefitinib has been granted a license for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK across all lines of therapy. AstraZeneca is required to conduct a follow-up measure study to generate more data in the caucasian NSCLC patient population.

8. Safety and tolerability

Gefitinib is generally well tolerated by all patients at the approved dosage of 250 mg/day . Adverse drug reactions (ADRs) usually are observed within the first month of therapy and are generally reversible. The most commonly reported ADRs were mild to moderate (grade 1/2) skin rash, diarrhoea and nausea, all of which were manageable and non-cumulative. Asymptomatic elevations in liver transaminases and bilirubin also occurred commonly but usually recovered upon discontinuation of therapy. Rarely did hepatitis occur. The frequency and severity of side effects increased at higher doses of gefitinib. Interstitial lung disease (ILD) has been reported as a recognized adverse event in 1% of patients receiving gefitinib worldwide, with death occurring in one in every three cases. Incidence is variable and tends to be highest in patients of Asian origin, particularly the Japanese (approximately 3%) [84,85]. This is compared with just 0.3% in the US expanded access programme [86]. Retrospective analyses of the incidence of ILD and prospective studies in Japan including 3000 patients, indicated male sex, previous smoking history and pre-existent ILD as risk factors for ILD development [84,87]. Mortality is greatest in those developing ILD with an associated smoking history, CT scan evidence of reduced normal lung capacity (≤ 50%), pre-existing ILD, older age (≥ 65 years), or extensive areas adherent to the pleura, independent of whether the ILD was induced by chemotherapy or gefitinib [84].

9. Regulatory affairs

Gefitinib is approved in 67 countries for use in advanced-stage NSCLC patients. Gefitinib was first approved in Japan in July 2002. Licensing in several other countries followed. In May 2003, gefitinib was granted accelerated approval by the FDA for use as monotherapy for patients with locally advanced or metastatic NSCLC after the failure of both

Table 3. Randomized Phase III trials in progress with gefitinib.

Study	Population	Treatment arm	Primary end point
EORTC08021	First-line maintenance for advanced NSCLC in patients without disease progression on completion of chemotherapy	Gefitinib vs placebo	OS
CAN-NCIC-BR19	First-line maintenance after complete resection of stage I – IIIA NSCLC ± adjuvant chemotherapy	Gefitinib vs placebo	OS
NCT01017874	First-line, East Asian, chemo-naïve, stage IIIb/IV, non-squamous histology. Never-smokers	Pemetrexed-cisplatin, maintenance gefitinib vs gefitinib	PFS
NCT00891579	Second-line, relapsed metastatic NSCLC, previous platinum therapy, EGFR-mutation-negative. Chinese population	Gefitinib vs pemetrexed	PFS

EGFR: EGF receptor; EORTC: European Organisation for Research and Treatment of Cancer; NSCLC: Non small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

platinum-based chemotherapy and docetaxel [40,41]. Use was subsequently restricted by the FDA in 2005 following the ISEL trial [44]. With restricted labelling, only those patients who had previously, or were currently deriving clinical benefit could receive gefitinib. A marketing authorization application to the EMEA was also withdrawn in January 2005. In 2008, data from the INTEREST and IPASS trials led to a resubmission for licensing. In June 2009 the EMEA granted marketing authorization for gefitinib treatment in patients with advanced or metastatic NSCLC, whose tumours bear EGFR-TK mutations, for any line of therapy in Europe.

10. Conclusion

Gefitinib is generally well tolerated and efficacy has been demonstrated in selected patients with advanced NSCLC. In untreated patients, selected on the basis of histology, smoking history and EGFR mutation status, gefitinib is associated with superior PFS compared with chemotherapy, therefore offering an additional first-line treatment option. Furthermore, overall survival achieved with gefitinib in relapsed advanced disease is not inferior to docetaxel.

11. Expert opinion

Gefitinib is the first targeted therapy in NSCLC for which the license mandates a molecular test in NSCLC, representing a major step towards the concept of personalized therapy in which treatment is selected on the basis of the molecular characteristics of tumour or host.

In chemotherapy-naive patients, the IPASS trial demonstrated the superiority of gefitinib compared to platinum-based chemotherapy in selected Asian patients [60] and concluded that gefitinib can be given first-line as an alternative to chemotherapy in never-smoking patients with adenocarcinoma tumours harbouring an EGFR mutation. This trial uniquely selected patients based on clinical characteristics known to enrich for a positive EGFR mutational status. Subsequent subset analysis found that EGFR mutation identified those most likely to respond and derive clinical benefit from gefitinib. Other Phase II and III studies conducted in East Asia established the role of these predictive biomarkers prospectively [61,62,88-90]. The relatively low frequency of EGFR mutation in the caucasian population, however, is still likely to limit the usage of gefitinib.

In a Western population, the INTEREST trial confirmed that survival with gefitinib therapy was not inferior to docetaxel chemotherapy in relapsed or refractory NSCLC [45]. Of particular relevance, gefitinib was less toxic and associated with enhanced quality of life. In light of these results, it is reasonable to consider gefitinib as an alternative to chemotherapy in previously treated NSCLC patients, especially, but not exclusively, for those with tumours harbouring an EGFR mutation. No demonstrable benefit has yet been found in combining gefitinib with chemotherapy in advanced NSCLC; however, a role as maintenance therapy is evolving. Early studies show improved PFS in favour of sequential gefitinib. Additional robust survival data are required and better insight as to the molecular characteristics of tumours in patients who benefit from maintenance therapy, in order to determine optimal drug sequencing (**Table 3**), both in advanced disease and the adjuvant setting.

Overall, the clinical development of gefitinib monotherapy has provided a proof of the principle of treatment selection based on molecular characteristics. The conduct of studies in unselected patients, coupled with intense efforts to collect tumour samples for molecular analyses, has led to the first license based on a molecular abnormality for a targeted agent in NSCLC. Gefitinib is a valuable option for selected patient subgroups as an alternative to first-line chemotherapy and as a consequence EGFR mutation testing is becoming a routine practice in the clinic.

Declaration of interest

F Blackhall and N Thatcher have received research support and honoraria from AstraZeneca and Roche. L Campbell declares no conflicts of interest.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Parkin DM, Bray F, Ferlay J. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899-909
3. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-18
4. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-23
5. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8
6. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51
7. Brabender J, Danenberg KD, Metzger R, et al. Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival. Clin Cancer Res 2001;7:1850-5
8. Fan Z, Mendelsohn J. Therapeutic application of anti-growth factor receptor antibodies. Curr Opin Oncol 1998;10:67-73
9. Rusch V, Klimstra D, Venkatraman E, et al. Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor alpha is frequent in resectable non-small cell lung cancer but does not predict tumor progression. Clin Cancer Res 1997;3:515-22
10. Herbst RS, Shin DM, Prager D, et al. Monoclonal antibodies to target epidermal growth factor receptor-positive tumors: a new paradigm for cancer therapy. Cancer 2002;94:1593-611
11. Sridhar SS, Seymour L, Shepherd FA. Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer. Lancet Oncol 2003;4:397-406
12. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171-7
13. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78
14. Cunningham D, Humblet Y, Siena S, et al. ĆCetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45
15. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-31
16. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32
17. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50
18. Manegold C, von Pawel J, Zatloukal P, et al. BO17704 Study Group. Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704. (ASCO Annual Meeting Proceedings Part I). J Clin Oncol 2007;25(20 June Suppl):LBA7514
19. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227-34
20. Culy CR, Faulds D. Gefitinib. Drugs 2002;62:2237-48; discussion 2249-50
21. Wakeling AE, Guy SP, Woodburn JR, et al. ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. Cancer Res 2002;62:5749-54
22. Baselga J, Rischin D, Ranson M, 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
23. Herbst RS, Maddox AM, Rothenberg ML, 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
24. Nakagawa K, Tamura T, Negoro S, 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 tumors. Ann Oncol 2003;14:922-30
25. Ranson M, Hammond LA, Ferry D, 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
26. Albanell J, Rojo F, Averbuch S, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. J Clin Oncol 2002;20:110-24
27. Bailey R, Kris M, Wolf M, et al. Tumor EGFR membrane staining is not clinically relevant for predicting response in patients receiving gefitinib ('Iressa', ZD1839) monotherapy for pretreated advanced non-small-cell lung cancer: IDEAL 1 and 2 [abstract LB-170]. 94th Annual Meeting of the

American Association of Cancer Research (AACR); 11–14 July 2003; Washington, USA

28. Di Gennaro E, Barbarino M, Bruzzese F, et al. Critical role of both p27KIP1 and p21CIP1/WAF1 in the antiproliferative effect of ZD1839 ('Iressa'), an epidermal growth factor receptor tyrosine kinase inhibitor, in head and neck squamous carcinoma cells. J Cell Physiol 2003;195:139-50
29. Moyer JD, Barbacci EG, Iwata KK, et al. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. Cancer Res 1997;57:4838-48
30. Ciardiello F, Caputo R, Bianco R, et al. Inhibition of growth factor production and angiogenesis in human cancer cells by ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor. Clin Cancer Res 2001;7:1459-65
31. Swaisland H, Laight A, Stafford L, 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
32. Swaisland HC, Ranson M, Smith RP, et al. Single-dose clinical pharmacokinetic studies of gefitinib. Clin Pharmacokinet 2005;44:1165-77
33. McKillop D, Partridge EA, Kemp JV, et al. Tumor penetration of gefitinib (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor. Mol Cancer Ther 2005;4:641-9
34. Haura EB, Sommers E, Becker A, et al. Pilot phase II study of preoperative gefitinib in early stage non-small cell lung cancer with assessment of intratumor gefitinib levels and tumor target modulation (ASCO Annual Meeting Proceedings Part I). J Clin Oncol 2007;25(18 Suppl):7603
35. McKillop D, McCormick AD, Miles GS, et al. In vitro metabolism of gefitinib in human liver microsomes. Xenobiotica 2004;34:983-1000
36. McKillop D, McCormick AD, Millar A, et al. Cytochrome P450-dependent metabolism of gefitinib. Xenobiotica 2005;35:39-50
37. McKillop D, Hutchison M, Partridge EA, et al. Metabolic disposition of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in rat, dog and man. Xenobiotica 2004;34:917-34
38. Swaisland HC, Ranson M, Smith RP, et al. Pharmacokinetic drug interactions of gefitinib with rifampicin, itraconazole and metoprolol. Clin Pharmacokinet 2005;44:1067-81
39. Baselga J, Averbuch SD. ZD1839 ('Iressa') as an anticancer agent. Drugs 2000;60(Suppl 1):33-40, discussion 41-2
40. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol 2003;21:2237-46
41. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149-58
42. Crino L, Cappuzzo F, Zatloukal P, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. J Clin Oncol 2008;26:4253-60
43. Goss G, Ferry D, Wierzbicki R, et al. Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status. J Clin Oncol 2009;27:2253-60
44. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-37

• **No overall survival benefit in heavily pretreated, unselected patients with advanced NSCLC compared with placebo.**

45. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809-18

•• **Gefitinib equivalent to docetaxel for overall survival, as treatment for relapsed, advanced NSCLC, unselected patients.**

46. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000l;18:2354-62
47. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103
48. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2010;28:744-52
49. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, ĆV-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008;26:4244-52
50. Cufer T, Vrdoljak E, Gaafar R, et al. 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
51. Lee DH, Park K, Kim JH, et al. Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res 2010;16:1307-14
52. Herbst RS, Giaccone G, Schiller JH, 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
53. Giaccone G, Herbst RS, Manegold C, 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
54. Casal J, Vázquez S, León L, et al. Erlotinib as maintenance therapy after concurrent chemoradiotherapy in patients (p) with stage III non-small cell lung

cancer (NSCLC): a Galician Lung Cancer Group phase II study. J Clin Oncol 2009;27(Suppl): abstract 7537

55. Cobo M, Martinez J, Montesa A, et al. Hospital Carlos Haya, Malaga, Spain. Phase II trial of erlotinib maintenance therapy after platinun-based chemotherapy in advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2009;27(Suppl): abstract e19013

56. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 2008;26:2450-6

57. Gray JR, Spigel DR, Hainsworth JD, et al. Maintenance gefitinib (G) after chemoradiotherapy (CRT) in patients (pts) with unresectable stage IIIA/B non-small cell lung cancer (NSCLC): a phase II trial of the Minnie Pearl Cancer Research Network. (ASCO Annual Meeting Proceedings Part I). J Clin Oncol 2006;24(18 Suppl):7188

58. Tsuboi M, Kato H, Nagai K, et al. Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer. Anticancer Drugs 2005;16:1123-8

59. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol 2009;28:753-60

• **Possible role for maintenance gefitinib. Improved progression-free, but not overall, survival in advanced NSCLC.**

60. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57

•• **Selected patients (Asian, adenocarcinoma, non-smokers) have significantly improved progression-free survival with gefitinib rather than chemotherapy.**

61. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8

62. Kobayashi K, Inoue A, Maemondo M, et al. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: a phase III study (002) by North East Japan Gefitinib Study Group. J Clin Oncol 2009;27(15 Suppl): abstract 8016

63. Lee JS, Park K, Kim S-W, et al. A randomized phase III study of gefitinib (IRESSATM) versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung. WCLC, PRS.4, 2009

•• **EGFR-mutation-positive patients have improved PFS when treated with gefitinib compared with chemotherapy.**

64. Janne PA, Gurubhagavatula S, Yeap BY, et al. Outcomes of patients with advanced non-small cell lung cancer treated with gefitinib (ZD1839, 'Iressa') on an expanded access study. Lung Cancer 2004;44:221-30

65. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol 2004;22:1103-9

66. Ho C, Murray N, Laskin J, et al. 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

67. Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. Int J Clin Oncol 2006;11:190-8

68. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67

69. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2009;28:744-52

70. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39

71. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500

72. Pao W, Miller V, Zakowski M, et al. Predicting sensitivity of non-small-cell lung cancer to gefitinib: is there a role for P-Akt? J Natl Cancer Inst 2004;96:1117-19

73. Takano T, Ohe Y, Sakamoto H, et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005;23:6829-37

74. Kwak EL, Sordella R, Bell DW, et al. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci USA 2005;102:7665-70

75. Kobayashi S, Boggon TJ, Dayaram T, et al. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. Cancer Res 2005;65:7096-101

76. Choong NW, Dietrich S, Seiwert TY, et al. Gefitinib response of erlotinib-refractory lung cancer involving meninges – role of EGFR mutation. Nat Clin Pract Oncol 2006;3:50-7; quiz 1 p following 57

77. Costa DB, Schumer ST, Tenen DG, Kobayashi S. Differential responses to erlotinib in epidermal growth factor receptor (EGFR)-mutated lung cancers with acquired resistance to gefitinib carrying the L747S or T790M secondary mutations. J Clin Oncol 2008;26:1182-4;author reply 1184-6

78. Lee DH, Kim SW, Suh C, et al. Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. Ann Oncol 2008;19:2039-42

79. Cho BC, Im CK, Park MS, et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 2007;25:2528-33

80. Vasile E, Tibaldi C, Falcone A. Is erlotinib really active after failure of gefitinib in advanced non-small-cell lung

cancer patients? Ann Oncol 2009;20:790-1

81. Bos JL. ras oncogenes in human cancer: a review. Cancer Res 1989;49:4682-9
82. Forbes S, Clements J, Dawson E, et al. Cosmic 2005. Br J Cancer 2006;94:318-22
83. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. Clin Cancer Res 2009;15:5267-73
84. Ando M, Okamoto I, Yamamoto N, 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
85. Nakagawa M, Nishimura T, Teramukai S, et al. Interstitial lung disease in gefitinib-treated Japanese patients with non-small cell lung cancer – a retrospective analysis: JMTO LC03-02. BMC Res Notes 2009;2:157
86. Ochs JJJG, Warner KL. Final survival and safety results for 21,064 non-small-cell lung cancer (NSCLC) patients who received compassionate use gefitinib in a U.S. expanded access program (EAP). J Clin Oncol (ASCO Annual Meeting Proceedings, Post-Meeting Edition) 2004;22(14 Suppl):7060
87. Kudoh S, Kato H, Nishiwaki 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
88. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-400
89. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced Cnon-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442-9
90. Sutani A, Nagai Y, Udagawa K, et al. Gefitinib for non-small-cell lung cancer patients with epidermal growth factor receptor gene mutations screened by peptide nucleic acid-locked nucleic acid PCR clamp. Br J Cancer 2006;95:1483-9
91. Yoshida K, Yatabe Y, Park JY, et al. Prospective validation for prediction of gefitinib sensitivity by epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer. J Thorac Oncol 2007;2:22-8

• **Early indication that EGFR mutation may select patients likely to benefit from gefitinib.**

92. Sunaga N, Tomizawa Y, Yanagitani N, 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;56:383-9
93. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol 2006;24:3340-6
94. Asahina H, Yamazaki K, Kinoshita I, 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
95. Sugio K, Uramoto H, Onitsuka T, et al. Prospective phase II study of gefitinib in non-small cell lung cancer with epidermal growth factor receptor gene mutations. Lung Cancer 2009;64:314-18
96. Tamura K, Okamoto I, Kashii T, 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
97. van Zandwijk N, Mathy A, Boerrigter L, et al. EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. Ann Oncol 2007;18:99-103

Affiliation

Lynn Campbell† MB ChB BMSc(Hons) MRCP, Fiona Blackhall MB ChB FRCP PhD & Nicholas Thatcher MB BChir PhD FRCP
†Author for correspondence
Christie Hospital NHS Foundation Trust, Medical Oncology,
Wilmslow Road,
Manchester M20 4BX, UK
Tel: +44 161 446 8568; Fax: +44 161 446 3299;
E-mail: lrcampbell@doctors.org.uk