Review

Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: Review of the evidence

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ABSTRACT

Gefitinib is a small molecule tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR). Since 2004, it was clear that a substantial proportion of non-small-cell lung cancers (NSCLC) obtaining objective response when treated with gefitinib harbour activating mutations in the *EGFR* gene. Consequently, *EGFR* mutation has been widely studied, together with other molecular characteristics, as a potential predictive factor for gefitinib efficacy. As of August 2010, four East Asian randomized phase III trials comparing gefitinib to platinum-based chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) eligible for first-line treatment have been reported or published. Two of these trials were conducted without a molecular selection in patients with clinical characteristics (adeno-carcinoma histology, never or light smoking) characterized by higher prevalence of *EGFR* mutation. In patients selected for the presence of tumor harbouring *EGFR* mutation, the administration of first-line gefitinib, as compared to standard chemotherapy, was associated with longer progression-free survival, higher objective response rate, a more favourable toxicity profile and better quality of life. The relevant improvement in progression-free survival with first-line administration of gefitinib has been confirmed in the other two randomized trials, dedicated to cases with *EGFR* mutation. In July 2009, European Medicines Agency granted marketing authorization for gefitinib for the treatment of locally advanced or metastatic NSCLC with sensitizing mutations of the *EGFR* gene, across all lines of therapy. Gefitinib currently represents the best first-line treatment option for this molecularly selected subgroup of patients.

1. Introduction

Since a landmark meta-analysis demonstrated a significant, although clinically modest, improvement in overall survival compared to best supportive care [1], platinum-based chemotherapy has been considered the standard first-line treatment for good performance status patients with advanced non-small-cell lung cancer (NSCLC).

Epidermal growth factor receptor (EGFR)-dependent pathway plays an important role in the development and progression of human epithelial cancers, including NSCLC. Activation of the EGFR pathway is able to promote tumor growth and progression, stimulating cancer cell proliferation, production of angiogenic factors, invasion and metastasis, and inhibiting apoptosis [2]. In the last decade, two small molecules, orally active, selective and reversible EGFR-tyrosine kinase inhibitors have been extensively developed in NSCLC: gefitinib and erlotinib.

In recent years, great efforts in clinical and laboratory research led to a better knowledge of predictive factors of the efficacy of these drugs. In particular, increasing evidence has been accumulated, supporting a strong predictive role of *EGFR* gene mutation in tumor cells. In parallel, EGFR inhibition strategy, that was originally limited to patients who had already failed previous standard treatment, has been tested as first-line strategy.

In this article, we review the evidence obtained with use of gefitinib in advanced NSCLC, with special focus on the recent randomized phase III trials that consistently support the role of gefitinib as first-line treatment option in molecularly selected patients.

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2. Administration of gefitinib in unselected patients pretreated with chemotherapy

The activity of gefitinib was originally tested in patients with advanced NSCLC after failure of one or two previous chemotherapy regimens, at least one containing platinum, in two randomized phase II trials [3,4]. Both trials showed encouraging activity, in terms of objective response rate and clinical benefit with symptomatic improvement. In 2003, based on those promising phase II data, gefitinib received accelerated approval by the FDA for patients with locally advanced or metastatic NSCLC, after failure of both platinum-based and docetaxel chemotherapies [5]. Subsequently, gefitinib was compared to placebo in the ISEL phase III trial, for patients with advanced NSCLC who had received one or two regimens of chemotherapy and who were refractory to or intolerant of their latest chemotherapy regimen [6]. In this study, 1692 patients were randomly assigned to receive either gefitinib (orally, 250 mg daily) or placebo, plus best supportive care. Patients were not selected according to any molecular characteristic. The primary end-point of the trial was overall survival, which was not significantly different between the groups, neither in the overall population nor among the 812 patients with adenocarcinoma. Due to these negative results, the license was removed in all world countries where it was available, except in Asia [7].

Several randomized phase II [8] or phase III [9–11] trials compared gefitinib to chemotherapy as second-line treatment in unselected patients. In the largest study, the INTEREST trial, 1466 patients in progression after one or two chemotherapy regimens were randomized to docetaxel or gefitinib [11]. The study met the primary endpoint of demonstrating non-inferiority of gefitinib related to docetaxel in terms of overall survival, in a population of patients not selected for molecular characteristics. A meta-analysis of all 4 existing trials comparing gefitinib to docetaxel produced pooled results that were consistent with the individual studies, with no difference in overall survival and progression-free survival, and a significant increase in chance of objective response [12].

3. Administration of gefitinib as first-line treatment of unselected patients

Despite promising preclinical results, showing that EGFR-tyrosine kinase inhibitors can enhance the anti-tumor activity of chemotherapy, two large randomized phase III trials, investigating the concomitant addition of gefitinib to first-line platinum-based chemotherapy of advanced NSCLC, followed by single-agent gefitinib until disease progression, produced negative results [13,14]. Of note, patients enrolled in these trials were not selected for any clinical or molecular characteristic.

Several phase II trials tested single-agent gefitinib as first-line treatment of unselected patients with advanced NSCLC [15–17]. In the phase II randomized study comparing gefitinib with vinorelbine in chemotherapy-naïve elderly patients with advanced NSCLC [17], gefitinib was associated with a better tolerability profile, and there was no statistical difference between the two treatments in terms of progression-free survival and overall survival.

4. Preliminary evidence about predictive factors of gefitinib efficacy

In 2004, several groups reported that a substantial percentage of NSCLC tumors obtaining objective response when treated with EGFR tyrosine kinase inhibitors (gefitinib or erlotinib) harbour activating somatic mutations in the EGFR gene [18–21]. In the first of these seminal publications, Lynch et al. [18] described somatic heterozygous mutations in the tyrosine kinase domain of

the EGFR gene in 8 out of 9 NSCLC patients that experienced long lasting partial responses after administration of gefitinib, whereas no mutation was found in 7 tumor samples derived from non-responsive patients. The described mutations were small in-frame deletions or amino-acid substitutions clustered around the ATP-binding pocket of the EGFR tyrosine kinase domain (in exons 18, 19 and 21). Similar data were provided by Paez et al. [19], that reported EGFR mutations in exons 19 or 21 in 5 out of 5 patients responding to gefitinib, as compared to no mutation found in non-responders. The frequency of somatic mutations within the tyrosine kinase domain of the EGFR gene was shown to be low in unselected Western patients with advanced NSCLC, but, interestingly, these mutations appeared to be much more frequent in Japanese and East Asian population. Furthermore, it was rapidly evident that some clinical or pathological characteristics are associated with higher prevalence of mutation: in detail, EGFR mutation is more frequent in never smokers, in women, and in patients with adenocarcinoma [22].

Based on this evidence, several small trials were conducted testing gefitinib as first-line treatment of patients selected for the presence of EGFR mutation [23–27], or selected according to other clinical or molecular putative predictive factors [28,29]. Although single-arm design prevented a definitive interpretation of efficacy, results of these preliminary trials were very promising, because gefitinib confirmed its good tolerability profile and was associated with objective response rate, progression-free survival and overall survival consistently better than it would have been expected with traditional chemotherapy.

5. Randomized phase III trials comparing gefitinib vs. platinum-based chemotherapy as first-line treatment

As of December 2010, four randomized phase III trials comparing gefitinib to platinum-based chemotherapy in patients with advanced NSCLC eligible for first-line treatment have been reported or published [30–33]. Characteristics of trial design are summarized in Table 1. All these trials have been conducted in East Asian countries. Patients assigned to experimental arm received oral gefitinib at the standard dose (250 mg daily). Patients assigned to chemotherapy arm received different platinum-based doublets (carboplatin plus paclitaxel in 2 trials [30,33], cisplatin plus gemcitabine in 1 trial [31] and cisplatin plus docetaxel in 1 trial [32]). Inclusion criteria of two trials [30,31] were based on a clinical selection: eligibility was restricted to patients with adenocarcinoma and never-smokers (and former light smokers in one trial [30]). This choice was obviously inspired by the previous evidence demonstrating high frequency of EGFR mutations, and high activity of gefitinib in NSCLC patients with these characteristics. The remaining two trials [32,33] were based on a molecular selection, and only patients with EGFR mutation positive tumor were eligible. Main clinical and molecular characteristics of patients enrolled in the 4 trials are summarized in Table 2.

5.1. Randomized phase III trials without biomarker-driven selection

The first randomized phase III trial comparing gefitinib vs. standard chemotherapy as first-line treatment of patients with advanced NSCLC was the IPASS (Iressa Pan-ASia Study) trial, conducted in 1217 Asian patients [30]. Patients were selected according to clinical factors known to be associated with higher prevalence of EGFR mutation (adenocarcinoma, including bronchioloalveolar carcinoma, and either never smokers or former light-smokers), but there was no selection based on EGFR mutation or other molecular markers (Table 1). The study was designed to demonstrate that gefitinib was non-inferior to chemotherapy

Table 1
Design of randomized phase III trials comparing gefitinib to platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC.

Study	Country	Inclusion criteria	Chemotherapy arm	Primary endpoint	Study hypothesis	Secondary endpoints	EGFR mutational analysis
Mok [30]	China Hong Kong Japan Taiwan Singapore Malaysia Philippines Thailand	Age > 18 Adenocarcinoma (incl. BAC) Non-smoker or former light smoker ECOG PS 0–2	Paclitaxel 200 mg/m^2 day 1 every 3 weeks + Carboplatin AUC 5–6 day 1 × 6 cycles	PFS	Non-inferiority of gefitinib (non-inferiority limit hazard ratio 1.2)	OS ORR Quality of life Safety EGFR mutations	Amplification refractory mutation system and DxS EGFR29 mutation-detection kit
Lee [31]	Korea	Age 18–75 Adenocarcinoma Never smoker ECOG PS 0–2	Gemcitabine 1250 mg/m^2 day 1 and 8 every 3 weeks + cisplatin 80 mg/m^2 day 1 × 9 cycles	OS	Superiority of gefitinib (hazard ratio 0.6)	ORR DCR PFS Quality of life Safety EGFR mutations	n.a.
Mitsudomi [32]	Japan	Age < 75 WHO PS 0–1 Activating EGFR mutation (exon 19 deletion or L858R in exon 21)	Docetaxel 60 mg/m^2 day 1 every 3 weeks + cisplatin 80 mg/m^2 day 1 × 3–6 cycles	PFS	Superiority of gefitinib (hazard ratio 0.56)	OS ORR Safety	The exon 19 deletion mutation was screened by fragment analysis and the L858R point mutation was screened by the Cycleave method, followed by confirmation by direct sequencing
Maemondo [33]	Japan	Age < 75 ECOG PS 0–2 Sensitive EGFR mutation absence of resistant EGFR mutation T790M	Paclitaxel 200 mg/m^2 day 1 every 3 weeks + Carboplatin AUC 6 day 1 × >3 cycles	PFS	Superiority of gefitinib (improvement in median PFS from 6.7 to 9.7 months)	OS ORR Time to PS deterioration Safety	PNA-LNA polymerase-chain reaction clamp method

BAC: bronchioloalveolar carcinoma; PS: performance status; AUC: area under concentration vs. time curve; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; DCR: disease control rate.

Table 2
Characteristics of patients enrolled in randomized phase III trials comparing gefitinib to platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC.

Study	Arm	Number of patients	Clinical characteristics			EGFR mutational status	
			Women (%)	Adenocarcinoma (%)	Never smokers (%)	Known (%)	Positive/ known (%)
Mok [30]	Gefitinib	609	484 (79.5%)	581 (95.4%)	571 (93.8%)	223 (36.6%)	132 (59.2%)
	Chemotherapy	608	481 (79.1%)	591 (97.2%)	569 (93.6%)	214 (35.2%)	129 (60.3%)
Lee [31]	Gefitinib	159	140 (88.0%)	159 (100%)	159 (100%)	53 (33.3%)	26 (49.1%)
	Chemotherapy	150	134 (89.3%)	150 (100%)	150 (100%)	43 (28.7%)	16 (37.2%)
Mitsudomi [32]	Gefitinib	86	59 (68.6%)	83 (96.5%)	61 (70.9%)	86 (100%)	86 (100%)
	Chemotherapy	86	60 (69.8%)	84 (97.7%)	57 (66.3%)	86 (100%)	86 (100%)
Maemondo [33]	Gefitinib	114	72 (63.2%)	103 (90.4%)	75 (65.8%)	114 (100%)	114 (100%)
	Chemotherapy	114	73 (64.0%)	110 (96.5%)	66 (57.9%)	114 (100%)	114 (100%)

in terms of PFS, that was the primary endpoint of the trial. The Investigators hypothesized that, in such a clinically selected group of patients, first-line therapy with gefitinib would be at least as effective as chemotherapy, showing superiority in terms of tolerability and quality of life. The predefined non-inferiority margin was a hazard ratio 1.2 in PFS for gefitinib compared to chemotherapy. Actually, not only predefined conditions to declare non-inferiority were satisfied, but study results demonstrated superiority of gefitinib compared to carboplatin and paclitaxel: hazard ratio for PFS was 0.74, 95% CI 0.65–0.85, $p < 0.0001$ (Table 3). Median PFS was similar (5.7 months vs. 5.8 months, for gefinitib and chemotherapy, respectively), due to the crossing shape of the Kaplan Meier curves, that showed a better outcome with chemotherapy in the first 6 months, but subsequently favoring gefitinib.

Subgroup analysis based on molecular analyses was conducted on the subset of patients with tumor sample available for molecular analysis (30–36% of the total sample). In the subgroup of 437 patients analyzed for the presence of *EGFR* mutation, there was a significant interaction between treatment efficacy and *EGFR* mutation status. Namely, gefitinib was significantly better than chemotherapy in terms of PFS in patients with *EGFR* mutated tumors (HR for PFS 0.48, 95% CI 0.36–0.64, $p < 0.0001$), whereas chemotherapy was significantly better in *EGFR* wild-type patients (HR for PFS 2.85, 95% CI 2.05–3.98, $p < 0.0001$). This interaction was statistically significant ($p < 0.001$).

As shown in Table 4, objective response rate was significantly better in the gefitinib group compared to chemotherapy (43.0% vs. 32.2%; odds ratio, 1.59; $p < 0.001$). In the subgroup of EGFR mutation positive cases, chemotherapy produced a higher response rate compared to negative cases, and this supports a higher chemosensitivity of these tumors. However, gefitinib produced a

significantly higher response rate (71.2% vs. 47.3%; odds ratio, 2.75; $p < 0.001$).

Overall survival data in the original publication were immature, based on 37% of deaths [30]. Final overall survival data, based on 78% of events, have been presented in October 2010 [34]. In the whole study population, median overall survival for patients assigned to gefitinib was 18.8 months, compared with 17.4 months for patients assigned to chemotherapy arm (HR 0.90, 95% CI 0.79–1.02, $p = 0.11$). (Table 5). The analysis of overall survival according to mutational status, based on a subgroup of patients, showed a HR for death with gefitinib of 1.00 (CI 0.76–1.33) in the subgroup with mutation and 1.18 (CI 0.86–1.63) in the subgroup without mutation.

In another phase III randomized clinical trial reported at the 2009 World Conference on Lung Cancer, the First-SIGNAL study, oral gefitinib confirmed an improvement in progression-free survival compared to first-line chemotherapy in patients with EGFR mutation [31]. The First-SIGNAL trial was conducted in Korea, and eligibility criteria were similar to the IPASS trial (Table 1). Overall, 313 patients with advanced NSCLC with adenocarcinoma who had never smoked were eligible; due to this clinical selection, nearly 89% of the patients were female (Table 2). Eligible patients were randomized to gefitinib or standard chemotherapy with cisplatin and gemcitabine. Overall survival, the primary endpoint of the study, was similar in both groups, failing to show the hypothesized superiority of gefitinib compared to chemotherapy. Progression-free survival results were similar to the IPASS trial. Median PFS was 6.1 months vs. 6.6 months for gefitinib and chemotherapy respectively, and a crossing-shape of the Kaplan Meier curves was observed, in favor of chemotherapy in the first months and gefitinib subsequently. Progression-free survival at 1 year was 20.3% in the gefitinib arm compared to 5% in the chemotherapy arm. Objective

Table 3
Progression-free survival results in randomized phase III trials comparing gefitinib to platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC.

Study	Number of patients	Progression-free survival			
		Number of events (%)	Experimental arm (gefitinib) Median PFS	Standard arm (chemotherapy) Median PFS	Hazard ratio
Mok (all patients) [30,34]	1217	950 (78.1%)	5.7 months	5.8 months	0.74 (95% CI 0.65–0.85), $p < 0.0001$
Mok (EGFR mut+)	261	208 (79.7%)	9.6 months	6.3 months	0.48 (95% CI 0.36–0.64), $p < 0.0001$
Mok (EGFR mut−)	176	158 (89.8%)	1.6 months	5.5 months	2.85 (95% CI 2.05–3.98), $p < 0.0001$
Lee (all patients) [31]	309	295 (95.5%)	6.1 months	6.6 months	0.813 (95% CI 0.641–1.031), $p = 0.044$
Lee (EGFR mut+)	42	n.a.	8.4 months	6.7 months	0.613 (95% CI 0.308–1.221), $p = 0.084$
Lee (EGFR mut−)	54	n.a.	2.1 months	6.4 months	1.517 (95% CI 0.880–2.615), $p = 0.071$
Mitsudomi [32]	172	n.a.	9.2 months	6.3 months	0.489 (95% CI 0.336–0.710), $p < 0.0001$
Maemondo [33]	228	n.a.	10.8 months	5.4 months	0.30 (95% CI 0.22–0.41), $p < 0.001$

EGFR: epidermal growth factor receptor; Mut+: mutation positive cases; mut−: mutation negative cases; PFS: progression-free survival; n.a.: not available; CI: confidence interval.

Table 4
Objective response rate in randomized phase III trials comparing gefitinib to platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC.

Study		Objective response rate		
	Number of patients	Experimental arm (gefitinib)	Standard arm (chemotherapy)	Odds ratio
Mok (all patients) [30]	1217	262 (43.0%)	196 (32.2%)	1.59 (95% CI 1.25–2.01), $p = 0.0001$
Mok (EGFR mut+)	261	94 (71.2%)	61 (47.3%)	2.75 (95% CI 1.65–4.60), $p = 0.0001$
Mok (EGFR mut−)	176	1 (1.1%)	20 (23.5%)	0.04 (95% CI 0.01–0.27), $p = 0.0013$
Lee (all patients) [31]	309	85 (53.5%)	68 (45.3%)	1.385 (95% CI 0.885–2.167), $p = 0.1533$
Lee (EGFR mut+)	42	22 (84.6%)	6 (37.5%)	9.167 (95% CI 2.109–39.847), $p = 0.002$
Lee (EGFR mut−)	54	7 (25.9%)	14 (51.9%)	0.325 (95% CI 0.103–1.021), $p = 0.051$
Mitsudomi [32]	172	36/58 (62.1%)	19/59 (32.2%)	3.445 (95% CI 1.609–7.376), $p < 0.0001$
Maemondo [33]	228	84 (73.7%)	35 (30.7%)	6.32 (95% CI 3.55–11.25), $p < 0.001$

EGFR: epidermal growth factor receptor; Mut+: mutation positive cases; mut−: mutation negative cases; CI: confidence interval.

response rate was higher in the gefitinib group, although difference was not statistically significant (53.5% vs. 45.3%; odds ratio 1.385; $p = .01533$).

In the First-SIGNAL trial, EGFR mutational status was known in a minority of patients ($n = 96$). In EGFR mutation positive cases, median progression-free survival was significantly higher for patients treated with gefitinib (8.4 months vs. 6.7 months), and proportion of patients without progression at 1 year was 34.6% with gefitinib, vs. 14.3% with chemotherapy. EGFR mutation positive cases obtained a significantly higher response rate with gefitinib compared to chemotherapy. Of note (Table 4), the response rate obtained with gefitinib in EGFR mutation negative patients was higher compared to the IPASS trial (25.9% compared to 1.1%), but it should be considered that in the Korean study mutation tests were not centralized, and this could have determined a higher false negative rate.

5.2. Randomized phase III trials with biomarker-driven selection

Two randomized phase III trials comparing gefitinib to chemotherapy as first-line treatment of patients with advanced NSCLC, selected by the presence of EGFR mutation, have been recently published, both conducted by Japanese institutions [32,33]. Both trials demonstrated a statistically significant and clinically relevant increase in progression-free survival with gefitinib compared to platinum-based chemotherapy.

In the WJTOG3405 trial conducted by the West Japan Oncology Group (WJOG) [32], patients were selected by the presence of EGFR mutations (either the exon 19 deletion or L858R point mutation). Due to molecular selection, study population was characterized by a prevalence of women (more than two thirds in both study arms), by a prevalence of never smokers (more than two thirds of patients in both study arms), and the vast majority of patients had adenocarcinoma (Table 2). Baseline characteristics were well balanced between the two treatment groups, with the exception of a different distribution of type of EGFR mutations in the two groups: in detail, there was an excess of exon 19 deletion mutations in the gefitinib arm (58.1%) compared with the chemotherapy arm (43.0%). Eligible patients were randomized to receive gefitinib or cisplatin plus docetaxel. The study reached its primary endpoint, with median PFS of 9.2 months and 6.3 months, in the experimental and standard arm, respectively (hazard ratio 0.489, 95% CI 0.336–0.710, $p < 0.0001$). In this trial, 71 patients had recurrent disease after previous surgical resection, whilst the remaining 101 patients had advanced disease at diagnosis. In both subgroups, progression-free survival in the arm treated with first-line gefitinib was longer than that in the arm treated with cisplatin plus docetaxel. Similarly, although interaction tests are not provided, there seems to be no relevant heterogeneity of treatment effect among subgroups according to gender, smoking status, type of laboratory determining mutational status (central laboratory vs. commer-

cial laboratory) and type of EGFR mutation (exon 19 deletion vs. L858R point mutation). A very high proportion of patients assigned to control arm crossed-over to gefitinib after disease progression (Table 5). Data of overall survival reported in the publication were still immature, being based on 27 events (only 16% of the study sample size). Difference between arms was not statistically significant: in detail, median overall survival was 30.9 months in the experimental arm, and still not reached in the control arm.

In the NEJ002 study conducted by the North-East Japan Study Group (NEJSG), patients were randomized to receive gefitinib or carboplatin plus paclitaxel [33]. Also in this trial, progression-free survival was chosen as the primary endpoint. Study was prematurely stopped in May 2009 following the results of a planned interim analysis that demonstrated a significant superiority for gefitinib compared to chemotherapy in terms of progression-free survival. At the final analysis, performed in December 2009, median PFS was 10.8 months in the experimental arm, compared to 5.4 months in the standard arm (hazard ratio 0.30, 95% confidence interval 0.22–0.41, $p < 0.001$). Difference in overall survival between study arms was not statistically significant: in detail, median overall survival was 30.5 months in the experimental arm, and 23.6 months in the control arm ($p = 0.31$). However, study protocol recommended that the crossover regimen be used as second-line treatment, and 95% of patients assigned to control arm received second-line gefitinib (Table 5).

6. Toxicity associated with first-line administration of gefitinib

Similarly to the good tolerability demonstrated in previous trials when used as salvage therapy, gefitinib appears to be well tolerated when administered as first-line treatment of patients with advanced NSCLC. Of note, in the IPASS trial, gefitinib was associated with a lower rate of severe adverse events (defined as grade 3 or 4 according to the Common Terminology Criteria for Adverse Events, 28.7% vs. 61.0% for gefitinib and chemotherapy, respectively), a lower rate of adverse events leading to discontinuation of the drug (6.9% vs. 13.6%), and a lower rate of dose modification due to toxic effects (16.1% for gefitinib vs. 35.2% for carboplatin and 37.5% for paclitaxel) [30]. Similarly, in the NEJ002 trial, gefitinib confirmed a significantly lower incidence of severe toxic effects compared to carboplatin plus paclitaxel (41.2% vs. 71.7%, $p < 0.001$) [33].

In all randomized trials comparing first-line gefitinib to platinum-based chemotherapy, toxicity profile of experimental treatment was, as expected, substantially different from toxicity reported with chemotherapy [30–33]. The most common adverse events in patients receiving gefitinib were cutaneous toxicity (skin rash, dry skin), diarrhoea and liver dysfunction, usually consisting in asymptomatic hypertransaminasemia. In the vast majority of cases, these events were mild or moderate in inten-

Table 5
Proportion of cross-over at disease progression and overall survival results in randomized phase III trials comparing gefitinib to platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC.

Study	Number of pts.	Proportion of cross-over at disease progression		Overall survival			
		Experimental arm (gefitinib)	Standard arm (chemotherapy)	Number of events (%)	Experimental arm (gefitinib) Median OS	Standard arm (chemotherapy) Median OS	Hazard ratio
Mok (all patients) [30,34]	1217	60% platinum-based chemotherapy (49% carboplatin + paclitaxel)	52% EGFR inhibitor (41% gefitinib)	954 (78%)	18.8 months	17.4 months	0.90 (95% CI 0.79–1.02)
Mok (EGFR mut+)	261	68% platinum-based chemotherapy	64% EGFR inhibitor	199 (76%)	21.6 months	21.9 months	1.00 (95% CI 0.76–1.33)
Mok (EGFR mut−)	176	n.a.	n.a.	156 (87%)	11.2 months	12.7 months	1.18 (95% CI 0.86–1.63)
Lee (all patients) [31]	309	n.a.	80.7%	182 (59%)	21.3 months	23.3 months	1.003 (95% CI 0.749–1.343) $p=0.428$
Lee (EGFR mut+)	42	n.a.	n.a.	n.a.	30.6 months	26.5 months	0.823 (95% CI 0.352–1.922) $p=0.648$
Lee (EGFR mut−)	54	n.a.	n.a.	n.a.	18.4 months	23.3 months	1.199 (95% CI 0.570–2.521) $p=0.632$
Mitsudomi [32]	172	19.8%	59.3%	27 (16%)	30.9 months	Not reached	1.638 (95% CI 0.749–3.582) $p=0.211$
Maemondo [33]	228	67.5%	94.6%	n.a.	30.5 months	23.6 months	n.a. ($p=0.31$)

EGFR: epidermal growth factor receptor; Mut+: mutation positive cases; mut−: mutation negative cases; OS: overall survival; n.a.: not available; CI: confidence interval.

sity, and severe adverse events were infrequent. On the contrary, as expected, patients assigned to gefitinib arm suffered significantly less haematological toxicity, emesis, fatigue, neurotoxicity, constipation and hair loss, compared to patients treated with platinum-based chemotherapy.

Among potentially life-threatening events described with the use of gefitinib, interstitial lung disease (ILD) was relatively uncommon: it was described in 16 patients (2.6%) in the IPASS trial [30], 2 patients (2.3%) in the WJTOG3405 trial [32], 6 patients (5.3%) in the NEJ002 trial [33]. Five of these 24 cases were lethal, and further 2 lethal cases of ILD were described in the 159 patients treated with gefitinib in the First-SIGNAL trial [31], leading to a total of 7 lethal ILD toxicities in the 967 patients overall evaluated in the 4 trials (0.7%).

7. Health-related quality of life of patients receiving first-line gefitinib

Health-related quality of life was among secondary endpoints of two randomized phase III trials comparing gefitinib vs. chemotherapy as first-line treatment [30,31].

In the IPASS trial, quality of life was assessed by periodical administration of the Functional Assessment of Cancer Therapy-Lung (FACT-L) [30]. In the overall study population, including both *EGFR* mutation positive and negative cases, the administration of gefitinib was associated with a significant improvement in global quality of life (total score reported at FACT-L) compared to chemotherapy: proportion of patients with sustained clinically relevant improvement was 48.0% vs. 40.8%, respectively (odds ratio 1.34, 95% CI 1.06–1.69, $p=0.01$). Gefitinib determined a better outcome also in the Trial Outcome Index (TOI), which represents the sum of the physical well-being, functional well-being, and lung-cancer subscale scores of FACT-L: proportion of patients with sustained clinically relevant improvement was 46.4% vs. 32.8%, with gefitinib and chemotherapy respectively (odds ratio 1.78, 95% CI 1.40–2.26, $p<0.001$). On the contrary, no statistically significant difference was observed between gefitinib and chemotherapy in terms of lung-cancer specific subscale (LCS) in the overall study population: proportion of patients with sustained clinically relevant improvement was 51.5% vs. 48.5%, respectively (odds ratio 1.13, 95% CI 0.90–1.42, $p=0.30$).

It is important to highlight that in the IPASS trial, similarly to activity and efficacy results, also effects on patients' quality of life showed a significant interaction with *EGFR* mutational status. In *EGFR* mutation positive cases, analysis of quality of life changes demonstrated a significant benefit for patients assigned to first-line gefitinib compared to standard chemotherapy, whilst the opposite was observed in patients with *EGFR* mutation negative tumors. In detail, a sustained, clinically relevant improvement in global QoL was observed in 70.2% of *EGFR* mutation positive patients treated with gefitinib, compared to 44.5% of patients receiving chemotherapy (odds ratio 3.01, 95% CI 1.79–5.07, $p<0.0001$). The analysis of Trial Outcome Index (TOI), confirmed a significant interaction with *EGFR* mutational status. In the subgroup of *EGFR* mutation positive cases, improvement in global QoL was observed in 70.2% of patients treated with gefitinib, compared to 38.3% of patients receiving chemotherapy (odds ratio 3.96, 95% CI 2.33–6.71, $p<0.0001$). Furthermore, the analysis of items related to lung cancer symptoms confirmed that higher proportion of *EGFR* mutation positive patients experienced a benefit in the gefitinib arm compared to chemotherapy (75.6% vs. 53.9%, odds ratio 2.70, 95% CI 1.58–4.62, $p=0.0003$). Of note, both in terms of global QoL and in terms of lung cancer symptoms, improvements with gefitinib were usually rapid.

In the First-SIGNAL trial, quality of life was assessed by EORTC quality of life questionnaires QLQ-C30 and LC-13 [31]. In the overall study population, including both EGFR mutation positive and negative cases, gefitinib was associated with significantly better global health status and, among functional domains, with better role function and social function, compared to standard chemotherapy. As for quality of life items related to side effects of treatment, gefitinib was associated with significantly lower impact of appetite loss, peripheral neuropathy and hair loss. Data about changes in lung cancer symptoms are still not available.

8. Predictive role of biomarkers on treatment effect

Out of the 1217 patients enrolled in the IPASS trial, there were 683 available tumor samples (56%), 565 histology and 118 cytology samples [35]. Among exploratory analyses planned in the trial, in addition to the *EGFR* mutational analysis that was available in 437 patients (36%), there were *EGFR* gene copy number determination by fluorescence *in situ* hybridization (FISH, available in 406 patients, 33%) and EGFR expression analysis (available in 365, 30%). This high attrition rate was due, in the majority of cases, to insufficient quantity of tumor tissue, absence of sample at study centers or availability of cytology only. Unfortunately, in patients with advanced lung cancer, the amount of tumor tissue available is often very small and inadequate for molecular analysis. Similarly to the IPASS study, when tissue availability is not mandatory for patient inclusion, the proportion of cases available for molecular analysis in clinical trials is always significantly smaller than the study sample size [36]. However, in the IPASS trial, for all the planned molecular evaluations, patients with evaluable samples had similar baseline characteristics compared to the overall study population, with similar distribution of age, gender, performance status, smoking status and tumor stage [35].

Among evaluated samples, 60% of cases were positive for *EGFR* mutation, 61% were positive for high *EGFR* gene copy number and 73% were positive for EGFR expression, with similar proportion in both treatment arms. As already discussed, *EGFR* mutational status was a very strong predictor of treatment effect on progression-free survival (treatment by *EGFR* mutation status interaction test, $p < 0.0001$), with a relevant superiority of gefitinib in mutated cases and a significant superiority of chemotherapy in cases without *EGFR* mutation. There was a significant interaction of treatment effect on progression-free survival also with *EGFR* gene copy number ($p = 0.0437$). Gefitinib was associated with a longer progression-free survival compared to chemotherapy in cases with high *EGFR* gene copy number (hazard ratio 0.66, 95% confidence interval 0.50–0.88, $p = 0.005$), whilst an opposite trend was seen in cases with low *EGFR* gene copy number (hazard ratio 1.24, 95% confidence interval 0.87–1.76, $p = 0.24$). Interestingly, post hoc explorative analyses suggested that this effect was driven by the overlap of high *EGFR* gene copy number with a positive *EGFR* mutation status. Interestingly, *EGFR* mutational status confirmed to be strongly predictive of treatment effect on progression-free survival also when considering only patients characterized by high *EGFR* gene copy number. Namely, hazard ratio for gefitinib compared to chemotherapy was 0.48 (95% CI 0.34–0.67) in *EGFR* mutation positive cases, and 3.86 (95% CI 2.09–7.09) in *EGFR* mutation negative cases. Predictive power of EGFR protein expression analysis by immunohistochemistry was unsatisfactory: treatment by EGFR expression status interaction test was not significant ($p = 0.21$). Similar results were produced analyzing predictive role of molecular markers on objective response rate, with a strong predictive power of *EGFR* mutation status, a weaker role of *EGFR* gene copy number determination and completely negative interaction with EGFR protein expression analysis. In synthesis, molecular analyses of the IPASS

trial showed that *EGFR* mutation status was the strongest predictive factor for the effect of gefitinib compared to platinum-based chemotherapy, in terms of progression-free survival and objective response rate.

Interestingly, predictive role of *EGFR* mutation on the effect of gefitinib compared to chemotherapy is supported by data of the INTEREST trial, comparing gefitinib to docetaxel in previously treated patients with advanced NSCLC [37]. Although no statistically significant treatment by EGFR mutation status was found when considering overall survival, that could have been significantly influenced by post-study treatments, *EGFR* mutation-positive patients had longer progression-free survival (hazard ratio 0.16; 95% CI 0.05–0.49; $p = 0.001$) and higher objective response rate (42.1% vs. 21.1%; $p = 0.04$), with gefitinib compared to docetaxel. On the contrary, there was no statistically significant difference between gefitinib and docetaxel in *EGFR* mutation negative patients.

Among *EGFR* mutations detected in the IPASS trial, exon 19 deletions were the most common in both treatment arms (50% and 57.4% of positive cases, in experimental and standard arm, respectively). Most of the remaining positive cases presented exon 21 L858R (48.8% and 36.4% in experimental and standard arm, respectively), with a minority of exon 20 T790M (3.8% and 4.7%) and other mutations (2.3% and 5.4%) [35]. There was no formal analysis of interaction of treatment effect according to type of mutation, although a subgroup analysis showed a significant prolongation of PFS for gefitinib compared to chemotherapy both in the exon 19 deletion and L858R mutation subgroups [38]. Interaction analysis was performed in the WJTOG3405 trial [32]. By protocol, patients enrolled in that trial presented either the exon 19 deletion or L858R point mutation. There was no significant interaction between type of mutation and treatment effect. Namely, gefitinib was clearly superior to chemotherapy in terms of PFS in both molecular subgroups: hazard ratio was 0.453 (95% CI 0.268–0.768) in cases with exon 19 deletion and 0.514 (95% CI 0.294–0.899) in cases with L858R.

Exon 20 T790M mutation accounts for approximately 50% of acquired resistance to EGFR TKIs [39]. Thus, if it is clear that this mutation is associated to lack of benefit from EGFR TKI when found during treatment or as the only mutation in treatment-naïve patients, less clear is the case when T790M is found together with sensitizing mutations in treatment-naïve patients. For instance, all three treatment-naïve patients enrolled in the IPASS trial who harbored both the EGFR exon 19 mutation and the T790M had durable tumor responses with first-line gefitinib [40]. However, at the present, there are no robust data to decide to treat or not with EGFR TKI treatment-naïve patients whose tumors harbour both a sensitizing mutation and T790M.

9. State of the art

In patients with advanced NSCLC selected for the presence of *EGFR* mutation, the administration of first-line gefitinib, compared to standard platinum-based chemotherapy, is associated with longer progression-free survival, higher objective response rate, a more favourable toxicity profile and better quality of life. This can be considered high-level evidence, coming from four prospective, randomized phase III trials [30–33], two of which were conducted specifically in patients with tumor harbouring EGFR mutation [32,33]. The relevant heterogeneity of treatment effect according to presence or absence of EGFR mutation shown in the IPASS trial, even in a study population selected for clinical characteristics known to be associated with higher incidence of mutation and higher chance of EGFR inhibitors activity, demonstrates that clinical selection is not useful for the correct choice of treatment,
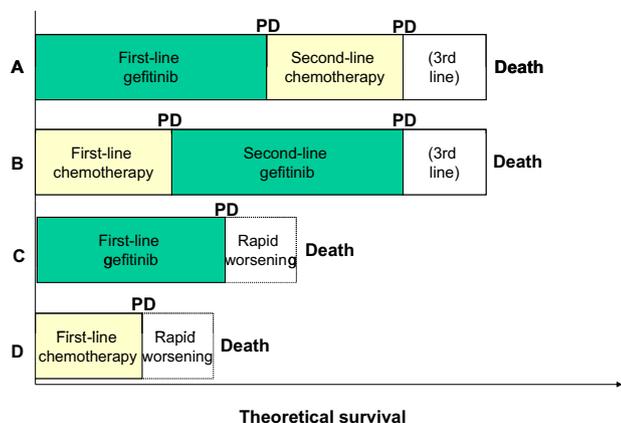
Fig. 1. Theoretical impact of treatment cross-over on overall survival of patients with *EGFR* mutation positive advanced NSCLC. Length of the bars is approximately proportional to median progression-free survival expected with each line of treatment. Patients A and B have better prognosis and receive both first-line and second-line (eventually third-line). Patients C and D have worse prognosis, experience a rapid symptomatic worsening after first-line treatment, and do not receive any second-line. PD: progressive disease.

that should instead be based on the molecular characterization. In July 2009, the EMEA granted marketing authorization for gefitinib for the treatment of locally advanced or metastatic NSCLC with sensitizing mutations of the *EGFR* gene, across all lines of therapy.

To date, none of these randomized trials demonstrated a statistically significant improvement with gefitinib in terms of overall survival (Table 5). Overall survival is of course the strongest endpoint for clinical research in oncology. However, differences in overall survival are potentially conditioned by cross-over, and a relevant number of patients assigned to chemotherapy arm received an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) as second- or third-line treatment after disease progression (Table 5). Intuitively, the high proportion of cross-over may extend to patients assigned to the control arm the benefit associated with the administration of gefitinib, and this "salvage" effect can compensate the relevant difference in progression-free survival of first-line treatment, consistently demonstrated in all trials (Fig. 1). In a series of Western patients with EGFR mutation positive NSCLC, treated with erlotinib, overall survival was similar for patients receiving the EGFR tyrosine kinase inhibitor as first-line or as second-line (median overall survival was 28.0 months and 27.0 months, respectively) [22]. However, the strategy of starting treatment with first-line chemotherapy and delaying the EGFR inhibitor at disease progression is associated with the risk that a patient with EGFR mutation could not be able to receive, at any point, an EGFR tyrosine kinase inhibitor, in case of rapidly progressive disease and worsening of physical conditions at first-line failure. Furthermore, prolongation of PFS could also be considered of value by itself, when the increase in life without progressive disease corresponds to a clinically relevant benefit, both in quantitative and qualitative terms. In patients with tumor harbouring EGFR mutation, administration of gefitinib as first-line demonstrated to produce higher symptomatic improvement, better quality of life and more favourable toxicity profile compared to chemotherapy. This should be strongly considered when choosing the first-line treatment for these patients considering that we should give for any patient the best treatment available at moment. Of course, patients with known EGFR mutation who did not receive gefitinib as first-line treatment should receive EGFR inhibitor in a subsequent line of treatment. Erlotinib was already approved as second- or third-line without molecular restrictions, whilst European marketing authorization for gefitinib is limited to patients with EGFR mutations, across all lines of therapy.

Other randomized phase III trials have been designed to test the efficacy of erlotinib, another anti-EGFR tyrosine kinase inhibitor, as first-line treatment of patients with EGFR-mutation positive tumors. The OPTIMAL phase III trial, conducted in China (ClinicalTrials.gov Identifier NCT00874419), comparing erlotinib (82 patients) to gemcitabine plus carboplatin (72 patients) was the first head-to-head comparison of erlotinib vs. chemotherapy in EGFR-mutation positive tumors to be presented [41]. Erlotinib was significantly superior to chemotherapy in terms of PFS, that was the primary endpoint: median PFS was 4.6 months with chemotherapy, compared to 13.1 months with erlotinib (HR 0.16, 95% CI 0.10–0.26, $p < 0.0001$). Erlotinib was superior also in terms of objective response rate (83% vs. 36%). Another study, the EURTAC trial, performed by the Spanish Lung Cancer Group (ClinicalTrials.gov Identifier NCT00446225) and recruiting patients from Spain, Italy and France, compares erlotinib to platinum-based treatment (cisplatin or carboplatin plus gemcitabine or docetaxel). The EURTAC trial has PFS as primary endpoint, with a planned enrolment of 146 patients. Results of this Western trial are awaited with great interest, because, differently from all the available trials that have been entirely conducted in Asia, it is conducted in Caucasian patients, and its results will add relevant evidence to this topic.

Afatinib (BIBW 2992) is a new, irreversible inhibitor of EGFR and erbB2 tyrosine kinase. Compared to placebo in patients who had failed previous chemotherapy and previous treatment with gefitinib or erlotinib, without molecular selection, afatinib demonstrated a significant prolongation of progression-free survival, although no significant benefit in overall survival was demonstrated [42]. In a phase II trial conducted in patients with EGFR mutation positive advanced NSCLC, afatinib produced a very high response rate and promising progression-free survival [43]. Given this high activity, results of two ongoing randomized phase III trials, comparing the efficacy of afatinib vs. platinum-based chemotherapy as first-line treatment in EGFR-mutated cases (ClinicalTrials.gov identifier NCT00949650 and NCT01121393), are awaited with great interest [44].

In recent years, we have learned that, from a biological point of view, NSCLC is a very heterogeneous disease. All the results that have been recently obtained with EGFR tyrosine kinase inhibitors in cases with *EGFR* mutation emphasize that not only heterogeneity is an important characteristic of tumor biology, but that it is also determinant for the chance of responding to and receiving substantial benefit from specific treatments. In the third millennium era, we should always try to obtain sufficient tumor tissue for histological subtyping and molecular testing. Personalized medicine for patients with lung cancer is now a reality, and patients with EGFR mutation should be treated with first-line EGFR tyrosine kinase inhibitor.

Conflict of interest statement

Acknowledgments

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