

Review Article

Gefitinib in Non Small Cell Lung Cancer

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Gefitinib is an oral, reversible, tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) that plays a key role in the biology of non small cell lung cancer (NSCLC). Phase I studies indicated that the recommended dose of gefitinib was 250 mg/day. Rash, diarrhea, and nausea were the most common adverse events. The positive results obtained in early phase 2 clinical trials with gefitinib were not confirmed in large phase 3 trials in unselected patients with advanced NSCLC. The subsequent discovery that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors prompted phase 2 and 3 trials with gefitinib in the first line-treatment of EGFR-mutated NSCLC. The results of these trials have demonstrated the efficacy of gefitinib that can be now considered as the standard first-line treatment of patients with advanced NSCLC harbouring activating EGFR mutations.

1. Introduction

Gefitinib (ZD1839, Iressa) is an orally administered, reversible tyrosine kinase inhibitor (TKIs) of epidermal growth factor receptor (EGFR), belonging to the smallmolecule class (quinazoline-derivative molecule) [1]. The EGFR family includes four different tyrosine kinase receptors: EGFR (ErbB-1), ErbB-2, ErbB-3, and ErbB-4 [2]. Each of these proteins has an extracellular ligand-binding domain, a single hydrophobic transmembrane domain and a cytoplasmic tyrosine kinase-containing domain. The receptors of the ErbB family are activated following binding to peptide growth factors of the EGF-family. Upon ligand binding, the ErbB receptors form either homo- or heterodimers and, following dimerization, auto- and transphosphorylation in tyrosine residues of the ErbB receptors occurs [3]. EGFR

signaling plays a key role in promoting the growth and survival of various types of solid tumors, including non small cell lung cancer (NSCLC) [4, 5].

Gefitinib has an inhibitory effect both on the autophosphorylation and downstream signaling, competing reversibly with the adenosine triphosphate (ATP) for the catalytic domain of EGFR. *In vitro* studies indicated that gefitinib potently inhibited EGFR tyrosine kinase activity at low concentrations that did not significantly affect other kinases tested [6]. *In vivo* studies showed that gefitinib had a favourable tolerability profile and an antitumor activity in various xenograft models and enhanced the antitumor activity of a variety of cytotoxic drugs, including platinum compounds [7, 8]. Gefitinib was well tolerated in healthy volunteers and showed a terminal half-life of 28 hours, supporting the once-daily oral administration [9].

This paper focuses on the clinical development of gefitinib in NSCLC, discussing the causes of its failure in unselected NSCLC patients and summarizing the available evidence coming from the randomized phase 3 trials that support the use of gefitinib as the standard first line treatment of patients with advanced NSCLC harbouring EGFR mutations.

2. Phase I Clinical Studies

Gefitinib has been evaluated as single agent in four phase 1 clinical trials, including patients with advanced refractory solid tumors. In the first study, conducted in UK and USA, gefitinib was administered once daily for 14 consecutive days, followed by 14 days off treatment [10]. Dose escalation started at 50 mg and continued to 925 mg or until consistent dose-limiting toxicity (DLT). Sixty-four patients were entered at eight dose levels. The most frequent dose-related grade 1 and 2 adverse events were acne-like rash, nausea, and diarrhea. Three of 9 patients treated at 700 mg/day developed DLT (reversible grade 3 diarrhea). Four of 16 patients with NSCLC had partial responses (observed from 300 to 700 mg/day). In the second study, including 88 patients in Europe and Australia, gefitinib was administered at dose ranging from 150 to 1000 mg/day in 28-day cycles to patients with either advanced non small cell lung, ovarian, head and neck, prostate, or colorectal cancer [11]. At 1000 mg/day, 5 of 12 patients experienced DLT (grade 3 diarrhea in four patients and grade 3 somnolence in one patient). The most frequent adverse events were acne-like rash (64%) and diarrhea (47%), which were generally mild (grade 1/2) and reversible on cessation of treatment. Nineteen patients had stable disease and received gefitinib for >3 months. In the third study, conducted in USA, 71 patients were enrolled at seven dose levels (ranging from 150 to 1000 mg/day in 28-day cycles) and most had NSCLC ($n = 39$) [12]. Diarrhea and rash, the primary DLTs, occurred at 800 mg. Frequent treatment-related grade 1-2 adverse events were diarrhea (55%), asthenia (44%), and acne-like follicular rash (46%). At doses >800 mg, 45% of patients required dose reductions. One partial response and 6 prolonged stable disease were observed in patients with NSCLC. The fourth phase 1 study investigated the tolerability and toxicity of gefitinib in Japanese patients with solid tumors [13]. Thirty-one patients were included and received oral gefitinib on 14 consecutive days, every 28 days. Dose escalation was from 50 mg/day to a maximum of 925 mg/day or DLT. The most frequent adverse events were an acne-like rash and gastrointestinal side effects. Two of 6 patients at 700 mg/day had DLT; no further dose escalation occurred. A partial response was observed in 5 of the 23 patients with NSCLC (duration 35–361 days) over a range of doses (225–700 mg/day), and 7 patients with various tumors had disease stabilization. Therefore, gefitinib showed a favourable tolerability profile and antitumor activity also in Japanese patients. Moreover, pharmacokinetic analyses from all these studies confirmed the feasibility of the once daily schedule.

The preclinical evidence of synergism between gefitinib and chemotherapy provided the rationale for a feasibility

study designed to assess the tolerability and antitumor activity of the combination of two doses of gefitinib (250 and 500 mg/day), gemcitabine and cisplatin (at standard doses) in chemotherapy-naïve patients with advanced or metastatic solid tumors, and to assess whether there was a pharmacokinetic interaction between these drugs when administered concurrently [14]. Eighteen patients were entered, 9 at each gefitinib dose level. Two patients developed DLT: one grade 3 convulsion (250 mg/day dose group) and one grade 3 rash (500 mg/day dose group). The most common grade 3/4 adverse events were vomiting (7 patients), asthenia (6 patients), thrombocytopenia (6 patients), diarrhea (5 patients), and anorexia (5 patients). Pharmacokinetic analyses showed no apparent pharmacokinetic interaction between gefitinib and cisplatin or gemcitabine, with the exception of a possible small increase in the geometric mean exposure to gemcitabine seen on day 8 of therapy when given alone with the higher dose of gefitinib. Of 10 evaluable patients with NSCLC, 5 had confirmed partial response, 4 had stable disease and 1 had progressive disease.

3. Development of Gefitinib in “Unselected” Patients

3.1. Phase II Clinical Studies. Two randomized phase 2 clinical studies evaluated the safety and the activity of two doses of gefitinib (250 mg or 500 mg) as second- or third-line therapy of NSCLC patients (IDEAL 1 and IDEAL 2) [15, 16]. The IDEAL-1 (Iressa Dose Evaluation in Advanced Lung cancer) study recruited 210 patients who were pretreated with one or two chemotherapy regimens, at least one containing platinum [15]. The IDEAL-2 study included 221 patients who were pretreated with two or more regimens containing platinum and docetaxel [16]. In both studies, the two doses of gefitinib produced similar results in terms of objective responses (approximately 20% in IDEAL-1 and 10% in IDEAL-2), disease control rate (about 50% in IDEAL 1 and 40% in IDEAL 2), and overall survival (about 8 months in IDEAL 1 and 7 months in IDEAL 2). Overall, the incidence of toxic effects, including skin rash and diarrhea, was lower in patients treated with 250 mg/day as compared with patients treated with 500 mg/day. These results led to choosing the lower dose for subsequent development of the drug in NSCLC. In both trials, an attempt has been made to identify predictive factors for objective response to gefitinib. In the IDEAL-1 study, a multivariate analysis showed that performance status, previous immuno/hormonal treatment, histology, and female gender were significantly associated with a higher response rate, while in the IDEAL-2 study only female gender was significantly predictive of response to gefitinib. The promising results of these trials led, in 2003, the Food and Drug Administration (FDA) to grant an accelerated approval for gefitinib as monotherapy treatment for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies.

The results of other phase 2 studies conducted with gefitinib as single agent in unselected patients with advanced NSCLC are summarized in Table 1 [15–23].

TABLE 1: Phase II clinical trials with Gefitinib as single agent in “unselected” NSCLC.

Author (yr)	Setting	Design	Pts	Gefitinib dose	Results	Toxicity
Fukuoka et al. (2003) [15]	Pretreated with 1-2 lines	Randomized phase 2	210	250 mg versus 500 mg	RR: 18.4% (250 mg) versus 19% (500 mg); PFS: 2.7 versus 2.8 months	Diarrhea, rash and other skin events
Kris et al. (2003) [16]	Pretreated with 2-3 lines	Randomized phase 2	221	250 mg versus 500 mg	RR: 12 versus 9%; OS: 7 versus 6 months	Diarrhea, rash and other skin events
D’Addario et al. (2008) [17]	Chemonaive	Phase 2, single arm	63	250 mg	RR: 9.5 %; DSR at 12 weeks: 38%	Rash and other skin events, hepatotoxicity
Wan et al. (2006) [18]	Not fit for chemo or pretreated	Phase 2, single arm	151	250 mg	RR: 29.8%; TTP: 12 months; 1 yr OS: 57%	Rash, diarrhea, nasal/oral mucosa bleeding
Lin et al. (2006) [19]	Chemonaive	Phase 2, single arm	53	250 mg	RR: 32.1%; TTP: 12 months; OS: 15.3 months; 1 yr OS: 57%	Skin toxicity, diarrhea, nail change, ILD
Niho et al. (2006) [20]	Chemonaive	Phase 2, single arm	42	250 mg	RR: 30%; OS: 13.9 months; 1 yr OS: 55%	Rash and other skin events, ILD
Reck et al. (2006) [21]	Chemonaive	Phase 2, single arm	58	250 mg	RR: 5%; TTP: 1.8 months; OS: 7.3 months	Skin toxicity and diarrhea
Suzuki et al. (2006) [22]	Chemonaive	Phase 2, single arm	34	250 mg	RR: 26.5%; OS: 14 months; 1 yr OS: 58.2%	Rash, fatigue, hepatotoxicity
Spigel et al. (2005) [23]	Chemonaive	Phase 2, single arm	70	250 mg	RR: 4%; TTP: 3.7 months; OS: 6.3 months; 1 yr OS: 24%	Rash and diarrhea

RR: response rate; PFS: progression-free survival; OS: overall survival; DSR: disease stabilization rate; TTP: time to progression; ILD: interstitial lung disease.

3.2. Phase III Clinical Studies in First-Line Therapy. The encouraging results obtained in early clinical trials and the preclinical evidence of synergism between gefitinib and chemotherapy prompted two large randomized phase 3 clinical trials examining the role of gefitinib in combination with standard chemotherapy (cisplatin plus gemcitabine in INTACT-1 and carboplatin plus paclitaxel in INTACT-2) for the first line treatment of advanced NSCLC [24, 25]. Both of these studies failed to demonstrate any advantage in overall survival for patients treated with chemotherapy in combination with gefitinib. Moreover, subgroups analyses of predictive factors of sensitivity to gefitinib did not demonstrate any survival advantage for specific subgroups when gefitinib was added to chemotherapy. Negative results were similarly observed with the combination of another tyrosine kinase inhibitor, erlotinib, with chemotherapy (TALENT and TRIBUTE studies) [26, 27]. Several explanations regarding the lack of an additive effect between tyrosine kinase inhibitors and chemotherapy have been proposed: a mechanistic interaction between gefitinib or erlotinib and chemotherapy, for which the antiproliferative effects of anti-EGFR agents may render tumor cells less sensitive to cytotoxic agents, as suggested by preclinical studies; the possibility that patients who benefit from EGFR-targeted treatments are the same who likely respond to chemotherapy; in this case, the effect of tyrosine kinase inhibitors can be masked by the effect of chemotherapy; finally, the lack of patient selection based on the expression of EGFR [28].

Because no additive effect was observed by administering gefitinib in combination with chemotherapy, a phase 3 trial was conducted to evaluate the efficacy of a sequential

strategy, with gefitinib given after first line platinum-doublet chemotherapy for NSCLC, which might have avoided problems of drug interference or antagonism [29]. Unfortunately, sequential gefitinib therapy after three cycles of standard platinum doublet chemotherapy showed no survival benefit over platinum doublet chemotherapy up to six cycles (HR 0.86, 95%CI 0.72–1.03, $P = .11$), although sequential gefitinib was associated with significantly prolonged progression-free survival (HR 0.68, 95%CI 0.57–0.80; $P < .001$). An exploratory subset analysis demonstrated a possible survival prolongation for sequential therapy of gefitinib, for patients with adenocarcinoma (HR 0.79, 95%CI 0.65–0.98, $P = .03$).

Table 2 summarizes the results of the randomized clinical trials with gefitinib in first- and second-line therapy, in locally advanced disease and adjuvant setting and in special populations [24, 25, 29–38].

3.3. Phase III Clinical Studies in Second-Line Therapy. A multicenter phase 3 study compared gefitinib as monotherapy at the dose of 250 mg/day to placebo in 1692 pretreated patients with NSCLC [30]. Patients treated with gefitinib reported significantly higher response rate (8% versus 1.3%) and longer time to treatment failure (3.0 versus 2.6 months). However, treatment with gefitinib was not associated with significant improvement in survival in the overall population (5.6 versus 5.1 months in the gefitinib and placebo arms, resp.) nor in the subgroup of patients with adenocarcinoma. There was pronounced heterogeneity in survival outcomes between groups of patients, with some evidence of benefit among never-smokers (median survival of 8.9 versus 6.1

TABLE 2: Randomized clinical trials with Gefitinib in unselected NSCLC.

Author (yr)	Setting	Design	Pts	Treatment	RR (%)	PFS (mos)	OS (mos)
Giaccone et al. (2004) [24]	Chemonaive	Phase 3	1093	CIS/GEM + gefitinib 500 versus CIS/GEM + gefitinib 250 versus CIS/GEM + placebo	50.3 versus 51.2 versus 47.2 <i>P</i> ns	5.5 versus 5.8 versus 6.0 <i>P</i> = .7633	9.9 versus 9.9 versus 10.9 <i>P</i> = .4560
Herbst et al. (2004) [25]	Chemonaive	Phase 3	1037	Carbo/taxol + gefitinib 500 versus Carbo/taxol + gefitinib 250 versus Carbo/taxol + placebo	30 versus 30.4 versus 28.7 <i>P</i> ns	4.6 versus 5.3 versus 5.0 <i>P</i> = .0562	8.7 versus 9.8 versus 9.9 <i>P</i> = .64
Takeda et al. (2010) [29]	Chemonaive	Phase 3	604	CIS/GEM × 3 → gefitinib versus CIS/GEM × 6	34.2 versus 29.3 <i>P</i> = .20	4.6 versus 4.3 HR: 0.68, 95% CI 0.57–0.80, <i>P</i> = .001	13.7 versus 12.9 HR: 0.86, 95% CI 0.72–1.03, <i>P</i> = .11
Thatcher et al. (2005) [30]	Pretreated with 1-2 lines	Phase 3	1692	Gefitinib 250 mg + BSC versus placebo + BSC	8 versus 1.3 <i>P</i> < .0001	3 versus 2.6 HR: 0.82, 95% CI 0.73–0.92, <i>P</i> = .0006	5.6 versus 5.1 HR: 0.89, 95% CI 0.77–1.02, <i>P</i> = .087
Cufer et al. (2006) [32]	Second line	Randomized phase 2	133	Gefitinib 250 mg versus Docetaxel 75 mg/mq	13.2 versus 13.7 HR 0.98, 95% CI 0.47–2.03	3 versus 3.4 HR: 0.94, 95% CI 0.64–1.39	7.5 versus 7.1 HR: 0.97, 95% CI 0.61–1.52
Kim et al. (2008) [33]	Pretreated with 1-2 lines	Phase 3	1466	Gefitinib 250 mg versus Docetaxel 75 mg/mq	9.1 versus 7.6 <i>P</i> = .33	2.2 versus 2.7 HR: 1.04, 95% CI 0.93–1.18, <i>P</i> = .47	7.6 versus 8.0 HR: 1.020, 95% CI 0.905–1.150
Maryuama et al. (2008) [35]	Pretreated with 1-2 lines	Phase 3	489	Gefitinib 250 mg versus Docetaxel 60 mg/mq	22.5 versus 12.8 <i>P</i> = .009	2 versus 2 HR: 0.90, 95% CI 0.72–1.12, <i>P</i> = .0335	11.5 versus 14 HR: 1.12, 95% CI 0.89–1.40, <i>P</i> = .330
D. H. Lee et al. (2010) [36]	Second line	Phase 3	161	Gefitinib 250 mg versus Docetaxel 60 mg/mq	28.1 versus 7.6 <i>P</i> = .0007	3.3 versus 3.4 HR 0.729, 95% CI 0.533–0.998, <i>P</i> = .0441	HR: 0.870, 95% CI 0.613–1.236, <i>P</i> = .4370
Crinò et al. (2008) [40]	Chemonaive ≥70 yrs	Randomized phase 2	196	Gefitinib 250 mg versus Vinorelbine 30 mg/mq 1–8	3.1 versus 5.1	2.7 versus 2.9 HR: 1.19, 95% CI 0.85–1.65	5.9 versus 8 HR: 0.98, 95% CI 0.66–1.47
G. Goss et al. (2009) [41]	Chemonaive PS 2-3	Randomized phase 2	201	Gefitinib 250 mg + BSC versus Placebo + BSC	6% versus 1% OR: 6.57, 95% CI 0.74–58.17	1.4 versus 1.3 HR: 0.82, 95% CI 0.60–1.12	3.7 versus 2.8 HR: 0.84, 95% CI 0.62–1.15
Kelly et al. (2008) [39]	Maintenance after chemo-radio Inoperable stage III	Phase 3	243	Gefitinib 500/250 mg versus Placebo	—	8.3 versus 11.7 HR: 0.80, 95% CI 0.58–1.10, <i>P</i> = .17	23 versus 35.0 HR: 0.633, 95% CI 0.44–0.91, <i>P</i> = .013
G. D. Goss et al. (2010) [38]	Adjuvant	Phase 3	503	Gefitinib 250 mg versus Placebo	—	4.2 yrs* versus nr HR: 1.22, 95% CI 0.93–1.61, <i>P</i> = .15	5.1 yrs* versus nr HR: 1.24, 95% CI 0.94–1.64, <i>P</i> = .14

CIS: cisplatin; Gem: gemcitabine; RR: response rate; PFS: progression-free survival; OS: overall survival; ns: not significant; nr: not yet reached; * disease-free survival.

months; HR 0.67; 95% CI 0.49–0.92, $P = .012$) and Asian ethnicity (9.5 versus 5.5 months; HR 0.66; 95% CI 0.48–0.91, $P = .01$). Explanations of the negative results of this trial could be the large number of chemotherapy refractory patients (90%), a suboptimal dose of gefitinib and the lack of selection based on potential molecular markers, associated with clinical outcome. In addition, exploratory biomarker analyses, including the assessment of EGFR gene copy number by FISH, EGFR and p-AKT protein expression by IHC, EGFR, K-RAS and D-RAF mutational status, showed a trend towards a better survival outcome for gefitinib in patients with high EGFR-gene-copy number (HR 0.61 for high copy number and HR 1.16 for low copy number, $P = .045$), while patients with EGFR mutations obtained higher RR than wild-type patients (37.5% versus 2.6%) [31]. No relationship was observed between p-AKT protein expression and survival outcome. On the basis of the lack of survival benefit in the ISEL study, in 2005 the FDA restricted the use of gefitinib to patients continuing to benefit from treatment already initiated or participating in clinical trials.

Four randomized trials compared gefitinib versus docetaxel as a second-line therapy of advanced NSCLC patients.

An open-label randomized phase 2 study (SIGN trial—Second line Indication of Gefitinib in NSCLC) compared gefitinib (250 mg/day) with docetaxel (75 mg/mq every 3 weeks) in 135 patients with advanced pretreated NSCLC [32]. Primary objective of this trial was symptom improvement using the FACT-L questionnaire. Gefitinib and docetaxel showed similar activity (symptom improvement rates of 36% and 26%, response rate of 13.2% and 13.7%, median progression-free survival of 3 and 3.4 months, median overall survival of 7.5 and 7.1 months, with quality of life improvement rates of 33.8% and 26% for gefitinib and docetaxel, resp.). However, gefitinib had a more favorable tolerability profile than docetaxel (adverse events of all grades: 51.5% versus 78.9%; grade 3–4: 8.8% versus 25.4%).

The INTEREST trial was the largest study comparing gefitinib to docetaxel as second- or third-line therapy in 1466 patients with advanced NSCLC treated with prior platinum-based chemotherapy [33]. The coprimary endpoints were the noninferiority of gefitinib in comparison with docetaxel in terms of overall survival in the total population and the superiority in patients expressing a high EGFR gene copy number. The study demonstrated the noninferiority of gefitinib (OS 7.6 versus 8.0 months, with a 1-year survival of 32% versus 34%, in the gefitinib and docetaxel arms, resp., HR 1.02, 96% CI 0.905–1.150, meeting the pre-defined non inferiority criterion of 1.154), while failed to demonstrate the superiority of gefitinib in the subgroup of 174 patients with high EGFR gene copy number: in this setting, median survival was 8.4 months in the gefitinib group and 7.5 months in the docetaxel group, and 1-year survival was 32 and 35%, respectively (HR 1.09; 95% CI 0.78–1.151, $P = .620$). The most common adverse events in the gefitinib group were skin reactions (49% versus 10%) and diarrhea (35% versus 25%), whereas in docetaxel group neutropenia (5% versus 74%), asthenia (25% versus 47%), and alopecia (3% versus 36%). Significantly more patients had sustained clinically relevant improvement in quality of life with

gefitinib than with docetaxel, as assessed by FACT-L total score (OR 1.99, 95% CI 1.42–2.79; $P < .0001$) and the FACT-L-TOI (OR 1.82, 95%CI 1.23–2.69; $P = .0026$). Similar proportions of patients had improvements in lung cancer symptoms (FACT-L LCS) with gefitinib and docetaxel (OR 1.29, 95%CI 0.93–1.79; $P = .013$). Moreover, a biomarkers analysis was conducted in this trial on 453 patients (31%) who had tissue samples evaluable for at least one biomarker (EGFR copy number by fluorescent in situ hybridization, EGFR protein expression by immunohistochemistry, and EGFR and KRAS mutations) and showed no difference in overall survival between treatments for any biomarker [34]. However, notably, among patients with EGFR mutation-positive tumors, PFS was longer (HR 0.16; 95% CI 0.05–0.49, $P = .001$) and objective response was higher (42.1% versus 9.8%) for gefitinib as compared to docetaxel. Overall survival was longer in patients with EGFR mutation-positive tumors in both gefitinib and docetaxel subgroups (median survival 14.2 and 16.6 months, resp.) than in the overall population (7.6 and 8.0 months, resp.) and in the population with wild-type EGFR (6.4 and 6.0 months, resp.), but there was no difference between treatments. Finally, exploratory analyses showed no difference between patients with high and low EGFR copy number within the gefitinib arm (high versus low HR, 1.02, 95% CI 0.74–1.41, $P = .914$) and no significant differences in survival outcome between the study arms according to KRAS mutation status.

Two further randomized phase 3 clinical trials (conducted in Japan and Korea, resp.) compared gefitinib versus docetaxel in patients with locally advanced or metastatic NSCLC, pretreated with one or two chemotherapy regimens [35, 36]. The Japanese trial did not meet the primary objective (non inferiority of gefitinib versus docetaxel) in terms of overall survival (11.5 months for gefitinib versus 14 months for docetaxel), although fewer severe adverse events (40.6% versus 81.6%) and benefits in terms of quality of life improvement occurred with gefitinib compared with docetaxel [35]. In the Korean study, gefitinib improved significantly objective response rate (28.1 versus 7.6%) and PFS (HR 0.73, 90% CI 0.53–0.98, $P = .0441$) than docetaxel [36]. However, no differences were observed in terms of OS (14.1 versus 12.2 months in the gefitinib and docetaxel arms, resp.) and quality of life or symptom improvement rates. A meta-analysis of the randomized clinical trials comparing gefitinib to docetaxel was presented at 2009 ASCO Meeting and showed similar overall and progression-free survival between the two drugs and superior response rate with gefitinib [37]. Therefore, given the similar efficacy demonstrated by gefitinib, its favorable tolerability profile, the quality of life benefits, and the oral administration, the Authors concluded that gefitinib has a favorable benefit-risk profile compared with docetaxel in a broad pretreated advanced NSCLC patient population.

3.4. Phase III Clinical Studies in Adjuvant and Locally Advanced Setting. A single phase 3 trial of adjuvant gefitinib has been conducted to date (the BR.19 trial), starting in the early 2000s, when a great enthusiasm existed for exploring the potential of this drug in NSCLC treatment [38].

In the BR.19 trial, patients with completely resected stage IB to IIIA NSCLC were randomly assigned to receive daily gefitinib 250 mg or placebo, for two years. They could also receive adjuvant chemotherapy as appropriate. The primary end-point was overall survival. The study planned to enrol 1160 patients, but it was stopped prematurely in 2005, following the negative results of the ISEL study [30] and the SWOG S0023 trials [39]. At the time of study closure, 503 patients had been enrolled. Data were presented at 2010 ASCO Annual Meeting. Median age of patients was 67; 54% were male, 54% PS 0 and most of them were ever smoker (89%); most of tumors were adenocarcinoma (59%); only 17% of patients received chemotherapy. Median followup was 4.7 years. Median time on treatment was 4.8 months in both arms. Differences were not significant for both overall survival (HR 1.24; 95% CI 0.94–1.64; $P = .14$) and disease-free survival (HR 1.22, 95% CI 0.93–1.61; $P = .15$), with a negative trend for gefitinib treatment. The toxicity analysis excluded the possibility of attributing this disadvantage to a higher incidence of fatal toxicity in the gefitinib arm. Preplanned subgroup analyses according to EGFR mutational status (357 evaluable patients, 76 of whom with mutation) demonstrated no benefit for gefitinib treatment in both wild-type and mutant NSCLC patients, with a more evident negative trend just in patients with EGFR mutations (HR 1.58, 95% CI 0.83–3.00; $P = .16$). Although all the comparisons have weak power due to the small number of the patients, these results are very striking and preclude the use of adjuvant gefitinib outside from clinical trials.

The above-mentioned SWOG S0023 trial [39] compared maintenance gefitinib to placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage IIIA and IIIB NSCLC patients. Overall survival was the primary end-point. This study also closed prematurely, on the recommendation of an unplanned interim analysis that was prompted by the results of the ISEL trial. Of the 571 eligible patients registered at the time of the interim analysis (against the 840 planned), 234 were randomized to receive gefitinib 500 mg or placebo, daily for five years. The interim analysis of this study showed that the hypothesized alternative of a 33% improvement in survival with gefitinib over placebo was ruled out with a one-sided $P = .0015$. Updated results, after a median followup of 27 months, were successively published, showing that patients receiving gefitinib had a worse survival than patients on placebo, with a median survival of 23 compared with 35 months (HR 0.63, 95% CI 0.44–0.91; $P = .013$). As in the BR.19 trial, the analysis of cancer-related and toxic death revealed that the inferior survival was due to tumor progression and not to gefitinib toxicity. Unfortunately, molecular features of the tumors, including EGFR mutations, were not recorded in this study. The detrimental effect of maintenance gefitinib after optimal cytoreduction with chemoradiotherapy in stage III NSCLC reported by the S0023 trial excludes the use of the drug in this setting of disease.

The evidence coming from these two randomized trials do not support the use of gefitinib in the localized stages of NSCLC patients, even with tumors carrying EGFR

mutations. The intrathoracic disease could have a different biologic behavior that should be further explored.

3.5. Randomized Clinical Studies in Special Populations. In consideration of its good toxicity profile, gefitinib has been tested as an alternative to a single-agent chemotherapy in elderly and poor performance status (PS) NSCLC patients. A randomized phase II trial was conducted by Crinò et al. with gefitinib (250 mg daily) versus vinorelbine in 196 untreated elderly (≥ 70 years) NSCLC patients [40]. The trial was designed to determine the superiority of gefitinib versus vinorelbine in terms of progression-free survival. The results showed no statistical difference in progression-free survival (2.7 versus 2.9 months, HR 1.19, 95% CI, 0.85–1.65, $P = .310$), overall survival (5.9 versus 8.0 months; HR 0.98, 95% CI, 0.66–1.47), and response rate (3.1 versus 5.1%) between gefitinib and vinorelbine, respectively. However, gefitinib showed a better toxicity profile. Most of the enrolled patients were male (77%), smokers (82%), and with squamous cell carcinoma, thus without clinical features conferring sensitivity to gefitinib, and this may explain the low percentage of responders in this study.

Goss et al. compared gefitinib to BSC in 201 untreated NSCLC patients with PS ≥ 2 , not eligible for chemotherapy, in a randomized phase II trial [41]. Primary endpoint was PFS and, nevertheless the results showed no statistical difference, there was a trend toward improved progression-free survival (HR 0.82, 95% CI, 0.60–1.12, $P = .217$), overall survival (HR 0.84, 95% CI, 0.62–1.15, $P = .272$) and response rate (6% versus 1% placebo) in favor of gefitinib.

4. Development of Gefitinib in “Selected” Patients

4.1. Phase II Clinical Studies. The recent discovery that some somatic mutations in the tyrosine kinase domain of the EGFR gene are associated with a high response to EGFR tyrosine kinase inhibitors in NSCLC highlighted the need for patient selection through molecular screening [42, 43].

Several phase 2 studies showed a high response rate (55–90%) and a prolonged progression-free survival (of approximately 9 months) with first-line gefitinib in Asiatic patients selected on the basis of the presence of activating EGFR gene mutations [44–56]. The results of these studies are summarized in Table 3. Yang and colleagues observed in 43 patients with exon 19 deletions and L858R mutations a response rate of 95% and 73.9% and a progression-free survival of 8.9 and 9.1 months, respectively [46]. The iTARGET trial selected chemo-naïve patients with nonsquamous histology who had one or more clinical characteristics associated with activating EGFR mutations, such as low or never smoking history, adenocarcinoma histology, female gender, and East Asian ethnicity [47]. In this study, mutations were identified in 35% of patients and 31 patients received gefitinib: the response rate was 55%, the median progression-free survival was 9.2 months, and overall survival was 17.5 months. Actually, the response rate was 78% and 59% for patients carrying L858R mutation and exon 19 deletion, respectively, which are activating

TABLE 3: Phase II trials with Gefitinib as single agent in “selected” patients with NSCLC.

Author (yr)	Setting	Pts	Treatment	Results	Toxicity
Asahina et al. (2006) [44]	Chemonaive, EGFR mutation	16	Gefitinib 250 mg	RR: 75%; PFS: 8.9 months, 1 yr OS: 88%	Rash, hepatotoxicity
Inoue et al. (2006) [45]	Chemonaive, EGFR mutation	16	Gefitinib 250 mg	RR: 75%; PFS: 9.7 months; 1 yr OS: 88%	Skin toxicity, stomatitis, diarrhea
Yang et al. (2008) [46]	Chemonaive, EGFR mutation	55	Gefitinib 250 mg	RR: 84.2%; PFS: 8.9 months, OS: 24 months	Skin toxicity, hepatotoxicity, diarrhea
Sequist et al. (2008) [47]	Chemonaive, EGFR mutation	31	Gefitinib 250 mg	RR: 55%; PFS: 9.2 months, OS: 17.5 months	Skin toxicity, diarrhea, nausea, fatigue
Sutani et al. (2006) [48]	1st-2nd line, EGFR mutation	27	Gefitinib 250 mg	RR: 78%; PFS: 9.4 months, OS: 15.4 months	Diarrhea, skin toxicity
Yoshida et al. (2007) [49]	Chemonaive, EGFR mutation	21	Gefitinib 250 mg	RR: 90%; TTP: 7.7 months	Skin toxicity, diarrhea, hepatotoxicity
Sunaga et al. (2007) [50]	Chemonaive, EGFR mutation	19	Gefitinib 250 mg	RR: 76%; DSR: 90%; TTP: 12.9 months	Skin toxicity
Tamura et al. (2008) [51]	Chemonaive, EGFR mutation	27	Gefitinib 250 mg	RR: 75%; DSR: 96%; PFS: 11.5 months, 1 yr OS: 79%	Skin toxicity, hepatotoxicity, stomatitis, diarrhea
Sugio et al. (2009) [52]	Chemonaive, EGFR mutation	19	Gefitinib 250 mg	RR: 63.2%; PFS 7.1 months, OS: 20 months	Skin toxicity, nail change
Inoue et al. (2009) [53]	Chemonaive, EGFR mutation and poor PS	30	Gefitinib 250 mg	RR: 66%, DSR 90%, PFS 6.5 months, OS 17.8 months, PS improvement rate: 79%	Hepatotoxicity, anemia, skin toxicity
Cappuzzo et al. (2007) [54]	FISH positive or never smokers	42	Gefitinib 250 mg	RR: 47.6%; PFS: 6.4 months; 1 y OS: 64%.	Skin toxicity, diarrhea
West et al. (2006) [55]	Brochoalveolar carcinoma, 1st-2nd line	91	Gefitinib 500 mg	RR: 9% and OS 13 months in 2nd line; RR 17% and OS 13 months in 1st line	Skin toxicity, diarrhea
D. H. Lee et al. (2005) [56]	Adenocarcinoma and never smokers	37	Gefitinib 250 mg	RR: 69%; PFS: 33 weeks; 1 yr OS: 73%	Skin toxicity, diarrhea

RR: response rate; PFS: progression-free survival; OS: overall survival; DSR: disease stabilization rate; TTP: time to progression.

mutations, predictive for response to gefitinib, whereas it was 0% in patients with atypical mutations. Therefore, this study has demonstrated that genotype-directed EGFR-TKI therapy with gefitinib for patients with previously untreated NSCLC is feasible also in a Western population. Inoue et al. tested gefitinib in a phase II trial in NSCLC patients harbouring EGFR mutations and with poor PS, not eligible for chemotherapy [53]. To note, 22 of 30 patients had very poor PS (3 or 4). The overall response rate was 66%, with disease stabilization rate of 90%. PS improvement rate was 79%. The median progression-free and overall survival were 6.5 and 17.8 months, respectively. This is the first report indicating that EGFR mutation-positive patients with poor PS can benefit from front line gefitinib treatment. Others phase II trials have selected patients on the basis of clinical, pathological, or molecular features. The ONCOBELL trial enrolled 42 patients who were never smokers or who had evidence of a high EGFR gene copy on FISH and were p-AKT positive [54]. The response rate was 47.6%, the median time to progression was 6.4%, and 1-year survival rate was 64.3%. In EGFR-mutated patients (66.8%), the response rate was 62.5%. The Southwest Oncology Group performed a phase II trial for pretreated ($n = 22$) or untreated ($n = 69$) patients with bronchioalveolar carcinoma [55]. The dose of

gefitinib used in this trial was 500 mg/day. The response rate in the pretreated and untreated patients was 9% and 17%, respectively. Finally, a phase II trial investigated the activity of gefitinib 250 mg daily in 37 chemo-naïve Korean patients with adenocarcinoma and a never-smoking history [56]. The response rate was 69% with a disease stabilization rate of 81%; median progression-free survival and 1-year survival rate were 33 weeks and 73%, respectively.

4.2. Phase III Clinical Studies. Four randomized phase III clinical trials evaluated the role of gefitinib as first line therapy of patients with advanced NSCLC, selected on the basis of clinical or molecular features (Table 4) [57–60]. The first evidence of efficacy of a therapeutic strategy based on an EGFR tyrosine kinase inhibitor as a first-line treatment of patients with advanced NSCLC derived from a large, randomized phase 3 clinical trial conducted in Asian patients, the IPASS study [57]. The IPASS (IRESSA Pan Asia Study) trial randomized 1217 patients with advanced adenocarcinoma, non-smoker or former light smoker, to receive gefitinib, 250 mg daily until progression or unacceptable toxicity, or carboplatin (AUC 5–6) plus paclitaxel (200 mg/m²) for a maximum of 6 cycles. The study met the primary objective (non inferiority of gefitinib) and

TABLE 4: Phase III trials with Gefitinib in “selected” NSCLC.

Author (yr)	Study	Setting	Pts	Treatment	RR (%)	PFS (mos)	OS (mos)
Mok et al. (2009) [57]	IPASS	1st line, clinically selected	1217	Gefitinib versus Carboplatin + Paclitaxel	43 versus 32.3 ($P = .0001$)	5.7 versus 5.8 HR: 0.74, 95% CI: 0.65–0.85, $P < .0001$	18.6 versus 17.3 HR: 0.91, 95% CI: 0.76–1.10
		Subgroup of EGFR mutated	261		71.2 versus 47.3 ($P < .001$)	9.5 versus 6.3 HR: 0.48, 95% CI: 0.36–0.64, $P < .001$	HR: 0.78, 95% CI 0.50–1.20
J. S. Lee et al. (2009) [58]	FIRST SIGNAL	1st line, clinically selected	309	Gefitinib versus Cisplatin + Gemcitabine	53.5 versus 45.3 ($P = .153$)	6.1 versus 6.6 HR: 0.813, 95% CI: 0.641–1.031, $P = .044$	21.3 versus 23.3 HR: 1.003, 95% CI: 0.749–1.343, $P = .428$
		Subgroup of EGFR mutated	42		84.6 versus 37.5 ($P = .002$)	8.5 versus 6.7 HR: 0.613, 95% CI: 0.308–1.221, $P = .084$	30.6 versus 26.5 HR: 0.823, 95% CI: 0.352–1.922, $P = .648$
Mitsudomi et al. (2010) [59]	WJTOG 3405	1st line, EGFR mutated	172	Gefitinib versus Cisplatin + Docetaxel	62.1 versus 32.2 ($P < .0001$)	9.2 versus 6.3 HR 0.489, 95% CI: 0.336–0.710, $P < .0001$	30.9 versus nr HR: 1.638, 95% CI 0.749–3.582, $P = .211$
Maemondo et al. (2010) [60]	NEJ002	1st line, EGFR mutated	230	Gefitinib versus Carboplatin + Paclitaxel	73.7 versus 30.7 ($P < .001$)	10.8 versus 5.4 HR 0.30, 95% CI: 0.22–0.41, $P < .001$	30.5 versus 23.6 $P = .31$

RR: response rate; PFS: progression-free survival; OS: overall survival; nr: not reached.

also demonstrated the superiority of gefitinib compared to carboplatin and paclitaxel in terms of progression-free survival in intention-to-treat analysis (HR 0.74, 95% CI: 0.65–0.85, $P = .001$). Because of the crossing of the curves, the median progression-free survival is similar with both treatments: however, the pattern of progression-free rates favors chemotherapy for the first 6 months and gefitinib for the remaining 16 months. The initial superiority of chemotherapy was attributed to the benefit that the EGFR-mutation-negative subgroup received from chemotherapy but not from gefitinib, whereas prolonged progression-free survival in the EGFR-mutation-positive subgroup explained the subsequent improvement favoring gefitinib. Crossing of the curves did not occur in the mutation-positive subgroup or the mutation-negative subgroup. Another important finding of this study was the significant interaction between treatment efficacy and EGFR mutational status. In the subgroup of patients with EGFR mutation (261 of 437 available samples), progression-free survival was significantly longer (HR 0.48; 95% CI 0.36–0.64, $P = .001$), and the response rate was significantly higher with gefitinib than with carboplatin-paclitaxel (71.2% versus 47.3%, $P = .001$). On the contrary, in the mutation-negative subgroup, progression-free survival was significantly shorter (HR 2.85; 95% CI 2.05–3.98, $P < .001$) and response rate was significantly lower with gefitinib (23.5% versus 1.1%, $P = .001$). Overall survival data were immature, based on only 37.0% of events, and showed a similar overall survival between the two groups: 18.6

months with gefitinib and 17.3 months with carboplatin-paclitaxel (HR for death in the gefitinib group, 0.91; 95% CI, 0.76 to 1.10). Final overall survival data confirmed no difference between gefitinib and chemotherapy, in the whole population (18.8 months with gefitinib versus 17.4 months with chemotherapy, HR 0.90, 95% CI: 0.79–1.02, $P = .11$) and in the mutation positive subgroup (HR 1.00, 95% CI: 0.76–1.33) [61]. Patients in the gefitinib group had a clinically relevant improvement in quality of life, as assessed by FACT-L questionnaire (OR 1.34; 95% CI 1.06–1.69, $P = .01$) and by TOI (Trial Outcome Index) scores (OR 1.78; 95% CI 1.40–2.26; $P < .001$). Moreover, gefitinib was associated with a lower rate of grade 3 or 4 adverse events compared to chemotherapy. The incidences of rash or acne, diarrhea, and elevated aminotransferase levels were significantly higher with gefitinib, whereas neurotoxic effects, nausea and vomiting, and hematologic toxic effects were significantly higher with carboplatin-paclitaxel. Interstitial lung disease events (i.e., the acute respiratory distress syndrome, interstitial lung disease, pneumonitis, or radiation pneumonitis) occurred in 16 patients treated with gefitinib (2.6%) and in 8 patients treated with chemotherapy (1.4%).

A second randomized phase 3 clinical trial compared gefitinib (250 mg daily) with cisplatin-gemcitabine as a first-line treatment in 309 Asian, never smokers patients, with advanced adenocarcinoma [58]. The study failed to reach its primary endpoint, overall survival, even if gefitinib allowed the achievement of a favorable response rate: 53.5% for

gefitinib versus 45.3% for chemotherapy (OR 1.385, 95% CI 0.885–2.167, $P = .153$). The overall mutation rate in this study was 43.8%: in mutation positive patients, the response rate was 84.6% for gefitinib versus 37.5% for chemotherapy ($P = .002$), while, in mutation negative subgroup, the response rate was 29.9% for gefitinib versus 51.9% for chemotherapy ($P = .051$). Median overall survival and progression-free survival were similar between the two groups. There was some difference in progression-free survival favoring gefitinib in mutation positive patients (8.5 versus 6.7 months; HR 0.613, 95% CI 0.308–1.221, $P = .0849$). There was no difference in overall survival by mutation status, both in the overall and EGFR-mutated populations: it could be due to the poststudy use of EGFR TKIs in 80.7% of chemotherapy arm.

Two randomized phase 3 studies have been performed in Japanese, EGFR-mutated patients with advanced NSCLC, to compare the efficacy of gefitinib versus chemotherapy in the first-line setting. In the open label phase III WJTOG3405 trial, 172 EGFR mutated patients were randomly assigned to receive gefitinib (250 mg daily) or chemotherapy (cisplatin 80 mg/m² plus docetaxel 60 mg/m² administered every 21 days for three to six cycles) [59]. The primary endpoint was progression-free survival. The study met its endpoint, showing a median progression-free survival of 9.2 months in the gefitinib group versus 6.3 months in the chemotherapy group (HR 0.489, 95% CI: 0.336–0.710, $P = .0001$). In this molecularly selected population, progression-free survival curves did not cross, unlike IPASS trial, being the benefit of gefitinib over chemotherapy consistent at any time of treatment. Response rate was 62.1% and 32.2% with gefitinib and chemotherapy, respectively ($P < .0001$). Myelosuppression, alopecia and fatigue were more frequent in the cisplatin-docetaxel group, while skin toxicity, liver dysfunction, and diarrhea in the gefitinib group.

Another prospective phase III study, the NEJ002 Trial, compared gefitinib to chemotherapy with carboplatin and paclitaxel as a first-line treatment in advanced NSCLC patients selected for EGFR mutation [60]. The study was stopped by independent data and safety monitoring committee after the preplanned interim analysis, conducted 4 months after the 200th patient enrolled, because it showed a significant difference in progression-free survival between the two treatment groups. The median progression-free survival was 10.4 months versus 5.5 months for gefitinib and chemotherapy, respectively (HR 0.36, 95% CI: 0.25–0.51, $P < .001$), and the final analysis confirmed these results, showing a median PFS of 10.8 versus 5.4 months for gefitinib and chemotherapy, respectively (HR 0.30, 95% CI 0.22–0.41, $P < .001$). The response rate was significantly higher in the gefitinib than chemotherapy arm (73.7% versus 30.7%, $P < .001$). The median progression-free survival and overall survival did not differ significantly between patients with exon 19 deletion and those with L858R point mutation (11.5 months versus 10.8 months, resp.). The overall survival did not differ significantly between the two treatment groups (median survival time and the 2-year survival rate were 30.5 months and 61.4% for gefitinib group as compared with 23.6 months and 46.7% for the chemotherapy, resp., $P = .31$).

Importantly, among 112 patients who had completed first-line carboplatin-paclitaxel, 106 (94.6%) received second-line gefitinib and 58.5% of these patients had a response. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase and, in the chemotherapy arm, appetite loss, neutropenia, anemia, and sensory neuropathy. Interstitial lung disease was reported in 6 patients (5.3%) in the gefitinib arm, with one of these fatal. In general, the incidence of severe toxic effects (NCI-CTC ≥ 3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% versus 41.2%, $P < .001$).

Therefore, these both studies confirmed gefitinib to be superior to chemotherapy in terms of response rate and progression-free survival in patients with EGFR mutations.

5. Ongoing Phase III/IV Studies in NSCLC

Several phase III/IV studies are currently ongoing with gefitinib in NSCLC in different clinical settings (Table 5).

A double-blind, multicenter, randomized, placebo-controlled phase III study is evaluating the efficacy, safety, and tolerability of gefitinib as a maintenance therapy in 296 patients with locally advanced or metastatic NSCLC (INFORM trial, ClinicalTrials.gov ID: NCT00770588). Patients must have completed 4 cycles of platinum-based first-line doublet chemotherapy without experiencing disease progression or unacceptable toxicity and are randomized to gefitinib or placebo at 1:1 ratio. The primary endpoint is progression-free survival; secondary endpoints are overall survival, objective tumor response, quality of life, and safety profile in terms of adverse events.

Another randomized phase III trial is evaluating the efficacy of a maintenance therapy with gefitinib compared with placebo in 600 Japanese patients treated with first-line chemotherapy for stage IIIB or IV NSCLC (ClinicalTrials.gov ID: NCT00144066). The primary aim of the study is to determine if gefitinib improves overall survival of the patients that did not progress on prior first line induction chemotherapy. Secondary objectives are progression-free survival and safety profile.

A phase IV study is investigating the activity and safety of gefitinib as first-line therapy for 100 Caucasian patients with EGFR-positive mutations (ClinicalTrials.gov ID: NCT01203917). The primary endpoint is the objective response rate; secondary endpoints are disease control rate, safety data, and overall survival.

A randomized phase III clinical study will compare gefitinib versus pemetrexed in never-smoker patients with adenocarcinoma histotype, previously treated with platinum-based chemotherapy (ClinicalTrials.gov ID: NCT01066195). The estimated enrollment is of 129 patients, and the main endpoints are progression-free survival, overall survival, objective response rate, and toxicity.

A randomized, open label, phase III study is enrolling 226 East Asian never or light ex-smoker patients with locally advanced or metastatic nonsquamous NSCLC, with the aim to compare first line cisplatin + pemetrexed for 6 cycles

TABLE 5: Ongoing phase III/IV studies in NSCLC.

Study phase	Line of treatment	ClinicalTrials.gov ID	Setting	Estimated sample size (pts)	Treatment	Primary endpoint
III	1st	NCT00770588	Maintenance after first line platinum-based chemotherapy	296	Gefitinib 250 mg versus Placebo	Progression-free survival
III	1st	NCT00144066	Maintenance after first line platinum-based chemotherapy	600	Gefitinib 250 mg versus Placebo	Overall survival
IV	1st	NCT01203917	Selected Caucasian pts	100	Gefitinib 250 mg	Objective response rate
III	≥2nd	NCT01066195	Never smoker pts with adenocarcinoma	129	Gefitinib 250 mg versus Pemetrexed	Progression-free survival
III	1st	NCT01017874	Selected East Asian pts	226	Gefitinib alone versus Cisplatin-Pemetrexed → Gefitinib	Progression-free survival
IV	1st	NCT00173524	First line Asian pts	200	Gefitinib versus Platinum-based chemotherapy	Cost-effectiveness
					Systemic and radiant	
III	1st-2nd	NCT00955695	Never smoker adenocarcinoma pts treated with prophylactic cranial irradiation	242	Prophylactic whole brain radiation therapy during gefitinib 250 mg or erlotinib 150 mg	Incidence of symptomatic brain metastases

followed by gefitinib for 6 courses (each of 21 days) versus gefitinib alone for 6 courses (each of 21 days) (ClinicalTrials.gov ID: NCT01017874). Primary endpoint is progression-free survival; secondary endpoints are overall survival, tumor response rate, disease control rate, time to progression, duration of response, and time to worsening of health-related quality of life. The trial should be completed in 2013.

A multicenter randomized phase III study is investigating the efficacy of whole brain radiation therapy compared with observation in preventing brain metastases in 242 patients with advanced NSCLC responding to first- or second-line gefitinib (250 mg/day) or erlotinib (150 mg/day) administered continuatively until disease progression or unacceptable toxicity (ClinicalTrials.gov ID: NCT00955695). Patients must be never smoker, with a diagnosis of adenocarcinoma with the EGFR-positive mutations on exon 19 or 21. Prophylactic cranial irradiation consists of 25 Gy cumulative dose over 10 fractions. The primary endpoint is the incidence of symptomatic brain metastases. Secondary endpoints are overall survival, progression-free survival, safety, psycho-neurological effects, and quality of life.

A phase IV pharmacoeconomics study will have the objective to analyze the cost-effectiveness and the cost-utility of gefitinib as a first-line treatment for 200 patients affected by stage IIIB or IV NSCLC, compared with the conventional first-line platinum-based chemotherapy (ClinicalTrials.gov ID: NCT00173524).

6. Discussion and Conclusions

The development of gefitinib in NSCLC is a clear example of the difficulties in designing and conducting of clinical trials with new molecular-targeted agents and of the uncertainty about predictive factors and selection criteria [62]. Crucial points, regarding the methodology of clinical research with target-based agents, especially for phase 3 trials, are how should patients be selected and which patients are expected to benefit from a targeted agent [63]. The proper characterization of a molecular target that allows the identification of responding versus nonresponding patients to a molecular-targeted agent could have important implications for the design of randomized trials evaluating the efficacy of the drug. In fact, the presence of unrecognized molecular heterogeneity can result in a falsely negative study that could be underpowered and may fail to detect a truly effective new therapy, leading to the rejection of a potentially useful drug [64].

Gefitinib was the first targeted drug that entered into clinical practice for the treatment of lung cancer: however, the positive results obtained in early clinical trials were not confirmed in large phase 3 trials, testing the efficacy of gefitinib in unselected patients with advanced NSCLC and, therefore, the use of gefitinib in clinical practice was stopped for several years.

It has been then shown that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase

inhibitors in patients with advanced NSCLC and that a substantial percentage of tumors with objective response to gefitinib or erlotinib harbours somatic mutations in the EGFR gene [42, 43, 65]. Moreover, clinical and demographic factors, including female sex, nonsmoking status, adenocarcinoma histotype, and Asian race have been identified as potentially predictive of the efficacy of EGFR tyrosine kinase inhibitors.

Currently, 4 randomized clinical trials have demonstrated the efficacy of gefitinib as a first-line treatment of NSCLC patients harbouring EGFR mutations: the IPASS and the First-SIGNAL studies, conducted in Asian patients selected for clinical factors; the WJTOG 3405 and the NEJ002 studies, conducted in patients selected for the presence of EGFR-activating mutations [57–60]. All these trials have demonstrated a statistically significant increase in progression-free survival with gefitinib compared to platinum-based chemotherapy in patients with EGFR-mutated advanced NSCLC. Moreover, treatment with gefitinib was associated with evidence of high objective response rate, better quality of life and more favourable toxicity profile. On these bases, in July 2009 gefitinib received from EMEA the authorization for the treatment of locally advanced or metastatic NSCLC with activating mutations of EGFR, across all lines of therapy and, currently, it can be considered the standard first-line treatment of patients with advanced NSCLC harbouring EGFR mutations.

Similar results have been recently obtained with erlotinib in a phase 3 clinical trial conducted in China (the OPTIMAL trial), comparing erlotinib to gemcitabine plus carboplatin, in EGFR-mutation-positive tumors in terms of progression-free survival [66]. The OPTIMAL study showed that erlotinib was significantly superior to chemotherapy in terms of progression-free survival (13.1 versus 4.6 months, HR 0.16, 95% CI: 0.10–0.26, $P < .0001$) and also in terms of objective response rate (83% versus 36%).

On the contrary, a treatment strategy based on a tyrosine kinase inhibitor (erlotinib) as a first-line therapy, followed at progression by chemotherapy in unselected patients with advanced NSCLC, is inferior to standard treatment with a first-line platinum-based doublet, followed at progression by erlotinib and cannot be recommended in clinical practice [67].

Several questions need to be addressed, regarding the reproducibility of these results in Western patients with NSCLC and EGFR mutations, the proper tyrosine kinase selection (gefitinib versus erlotinib), the lack of a survival benefit with first-line gefitinib in all these studies, the most appropriate clinical use of TKIs in mutated patients (first versus second line), the efficacy of gefitinib as neoadjuvant therapy or in combination with radiotherapy in patients with locally advanced NSCLC and EGFR mutations, and overcoming resistance to tyrosine kinase inhibitors. A large randomized phase 3 trial (the EURTAC trial, ClinicalTrials.gov ID NCT00446225) testing erlotinib in Western patients harbouring EGFR mutation is addressing the first question. Conversely, there are no ongoing phase 3 trials that directly compare gefitinib with erlotinib: therefore, the choice of the tyrosine kinase inhibitor to use in clinical practice should

be based on evidence coming from these randomized trials. Whether progression-free survival prolongation translates into survival gain is not yet clear: mature data from the IPASS trial showed no survival difference between first-line gefitinib and chemotherapy, probably due to treatment crossover of patients with tumor harbouring EGFR mutation [61].

The lack of a survival benefit with first-line gefitinib raises the question regarding its use as first- or second-line therapy, in patients selected by the presence of EGFR mutation. Data from Western and Asian patients suggest that there was no statistically significant difference in overall survival between patients receiving EGFR inhibitors as a first-line therapy or after failure of previous chemotherapy [68, 69]. However, these analyses were not based on a prospective comparison between the two strategies (first-versus the second-line therapy with EGFR inhibitors). Moreover, it should be considered that, for patients who do not receive first-line tyrosine kinase inhibitors, there is the risk of never receiving an EGFR inhibitor at the time of disease progression, due to a rapid worsening of clinical conditions. Finally, the better quality of life and more favourable toxicity profile with first line gefitinib, in addition to the prolonged progression-free survival, compared to chemotherapy, strongly support the use of gefitinib as a first-line therapy in patients with activating EGFR mutations.

The final results of ongoing clinical trials should define the efficacy of gefitinib also as neoadjuvant therapy or in combination with radiotherapy in patients with locally advanced NSCLC and EGFR mutations, while the development of irreversible inhibitors of EGFR tyrosine kinases [70] may have the potential to overcome the resistance to tyrosine kinase inhibitors.

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