Afatinib, Erlotinib and Gefitinib in the First-Line Therapy of EGFR Mutation-Positive Lung Adenocarcinoma: A Review

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Keywords

EGFR mutation · Adenocarcinoma · First-line therapy · EGFR TKI · Erlotinib · Gefitinib · Afatinib

Summary

Non-small cell lung cancer (NSCLC) consists of several histomorphologically defined phenotypes that display an enormous genetic variability. In recent years, epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma has emerged as a unique subset of NSCLC in terms of etiopathogenesis and tumor biology. Since the introduction of the reversible EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib, patients with metastatic EGFR mutation-positive lung cancer can be offered a therapeutic alternative that has proven its superiority over standard platinum-based chemotherapy. However, primary or acquired resistance limits the therapeutic success of these targeted agents. Irreversible inhibitors targeting all ErbB family receptor tyrosine kinases, such as afatinib and dacomitinib, have been developed to confer sustained disease control in ErbB-dependent cancers. The large LUX-Lung 3 phase III trial recently reported afatinib to be clearly superior over the most effective platinum doublet in patients with EGFR mutation-positive lung cancer. To fully exploit the clinical activity of afatinib, proactive management of its gastrointestinal and dermatologic toxicities is advised.

Schlüsselwörter

EGFR-Mutation · Adenokarzinom · Erstlinienbehandlung · EGFR TKI · Erlotinib · Gefitinib · Afatinib

Zusammenfassung

Nichtkleinzellige Lungenkarzinome (NSCLC) umfassen verschiedene histomorphologische Subtypen, die eine große genetische Heterogenität aufweisen. Epidermaler Wachstumsfaktorrezeptor (EGFR)-mutierte Adenokarzinome der Lunge wurden in den letzten Jahren aufgrund ihrer einzigartigen Ätiopathogenese und Tumorbilologie als eigenständige Subentität innerhalb der NSCLC identifiziert. Seit Einführung reversibler EGFR-Tyrosinkinaseinhibitoren (TKIs) profitieren Patienten mit metastasierten EGFR-mutierten Lungenkarzinomen von den Medikamenten Erlotinib und Gefitinib, die der Standardtherapie aus Platin-basierten Kombinationschemotherapien überlegen sind. Der Erfolg dieser zielgerichteten Medikamente wird jedoch durch primäre und erworbene Resistenzen eingeschränkt. Um bei ErbB-abhängigen Tumoren auch weiterhin eine Tumorkontrolle zu erreichen, wurden Inhibitoren wie Afatinib und Dacomitinib entwickelt, die sämtliche Rezeptoren der ErbB-Familie irreversibel blockieren. Die kürzlich veröffentlichten LUX-Lung-3-Phase-III-Studiendaten zeigen eine deutliche Überlegenheit von Afatinib gegenüber der derzeit effektivsten Platin-basierten Kombinationschemotherapie bei Patienten mit EGFR-mutierten Adenokarzinomen der Lunge. Um die volle klinische Aktivität von Afatinib nutzen zu können, ist eine aktive Behandlung der gastrointestinalen und dermatologischen Nebenwirkungen erforderlich.

Introduction

Lung cancer is the leading cause of cancer-related mortality and contributes to more than 1 million deaths every year

worldwide. Smoking is the main risk factor, but global statistics estimate that – considering vast regional variations – about 15% of lung cancer deaths in men and up to 50% in women will occur in lifelong never-smokers [1, 2]. This

makes non-smoking-related lung cancer one of the 10 most common deadly cancers if considered as an independent entity. Furthermore, due to smoking cessation and prevention initiatives, never-smokers and former smokers will constitute a larger part of the overall lung cancer population in the future. In metastatic non-small cell lung cancer (NSCLC), different platinum-based chemotherapy regimens offer a moderate clinical benefit, with response rates of 20–35% and a median survival time of 10–12 months. Unfortunately, there have been only small improvements in long-term survival over the past decades [3]. This is, at least in part, due to the enormous biologic and genetic heterogeneity of the disease, which has traditionally been therapeutically addressed with a ‘one-size-fits-all’ approach. Against this simplistic view, there has been much interest in personalizing treatment concepts for lung cancer patients in recent years. This was stimulated by a tremendous gain in knowledge of genetic alterations in lung cancer cells and the successful examples of imatinib as a genotype-directed drug for *bcr-abl*-positive leukemias and *c-kit* mutation-positive gastrointestinal stroma tumors (GIST). This established a new paradigm of oncogene-targeted therapies in oncology [4, 5]. Oncogenes code for proteins that are important for cell fate determinations and proliferation. They become activated during the multi-stage process of tumor-initiating events and/or tumor progression [6]. Once activated, oncogenes may render the cancer cell highly dependent on continued oncogene signaling, a phenomenon that is termed ‘oncogene dependency’ or ‘oncogene addiction’. Weinstein and others first postulated that critical oncogenes may therefore represent a deadly weakness of the tumor – metaphorically speaking, the cancer’s ‘Achilles heel’ – and a promising cellular target for cancer therapy [7].

In NSCLC and other epithelial malignancies, the epidermal growth factor receptor (EGFR) – first isolated by Stanley Cohen in 1962 [8] – as a member of the Her/ErbB receptor family has been identified as such a critical oncogene. Whereas non-malignant cells engage stringent regulatory programs for receptor tyrosine kinase (RTK) functions, the EGFR activity in cancer cells can be dysregulated by oncogenic mechanisms including increased *EGFR* gene copy number, EGFR overexpression, and activating gene mutations. This results in autophosphorylation of the cytoplasmic receptor domain and subsequently activates downstream signaling cascades including the mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), and Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathways, amongst others [9]. These activated pathways may ultimately counteract apoptosis and enhance cellular metabolism and cell proliferation. They also impinge on metastatic spread, angiogenesis, and resistance to anti-neoplastic agents or radiotherapy, thereby conferring an inferior prognosis in many solid tumors [10, 11]. Thus, the deregulated EGFR is a promising cellular target for the treatment of solid tumors and for lung cancer in particular.

Although the first anti-EGFR drugs were developed in the 1980s, small-molecule EGFR tyrosine kinase inhibitors (TKIs) like erlotinib (Tarceva®, Roche Pharma AG, Grenzach-Whylen, Germany) and gefitinib (Iressa®, AstraZeneca, Wedel, Germany) became clinically available for NSCLC treatment only during the last decade. Recently, afatinib (Gilotrif®, Boehringer Ingelheim GmbH, Ingelheim, Germany), a first-in-class irreversible ErbB family blocker, has been added to this therapeutic armamentarium [12–14].

EGFR Mutation-Positive Lung Adenocarcinoma – a Distinct Subset of Lung Cancer with Responsiveness to EGFR TKIs

Lung tumors exhibit frequent genetic and epigenetic aberrations with an, on average, 10-fold higher overall mutation frequency in smokers than in never-smokers [15]. EGFR is highly expressed on the cell surface of a substantial percentage of smoking- and non-smoking-related NSCLC (> 60%) [16], but only few tumors harbor activating *EGFR* gene mutations [17]. The etiology of these mutations still remains unknown; however, at least in some cases, they seem to represent an early carcinogenic event. They are not merely found in the tumor itself, but also in normal respiratory epithelium of lung cancer patients, in atypical adenomatous hyperplasia, in lung cancer founder clones, and in rare cases even in the germ line [18–20]. Since their initial description in 2004 [17, 21], many of these activating mutations have been discovered; they are all found in the first 4 exons [18–21] of the RTK domain. In-frame deletions in exon 19 (conferring a loss of 9–24 base pairs) and point mutations in exon 21 (leading to a base substitution of arginine to leucine at residue 858) are clinically most relevant, representing about 85–90% of all *EGFR* mutations [22]. In unselected patients, clinicopathological features like adenocarcinoma histology (40% vs. 3% in other histologies), East Asian descent (30% vs. 8% in non-Asians), female sex (42% vs. 14% in male patients), and particularly never-smoking status (51% vs. 10% in current or ever-smokers) are associated with an increased *EGFR* mutation frequency within the tumor [23]. Therefore, it has been postulated that they can serve as surrogates for the molecular marker. Furthermore, the mutation frequency is higher in the micropapillary-predominant and the lepidic-component adenocarcinoma subtypes [24]. Because of the strong association to the non-smoking status, *EGFR* mutation-positive lung adenocarcinoma and lung cancer in never-smokers as such are nowadays considered as distinct biological tumor subsets in the view of molecular pathogenesis [25]. Affected patients appear to have a better prognosis even when they are treated with cytotoxic chemotherapy [26–28]. In contrast to patients with *EGFR* wild-type tumors, they benefit from EGFR TKI treatment in terms of higher objective response rates (ORR), longer progression-free

survival (PFS), and/or longer median overall survival (OS) times [17, 21, 22, 29]. This is at least in part due to a higher TKI potency against mutant EGFR compared to wild-type EGFR in terms of ATP competition [30] and the absence of activating *KRAS* mutations, which usually occur after a substantial cigarette abuse and lead to EGFR TKI resistance [31]. The socio-economic impact of lung adenocarcinoma will prospectively increase in the future, as there has been accumulating evidence on sustained rising incidence rates in Asian and non-Asian populations for several decades, presumably due to changes in smoking habits and exposure to environmental carcinogens [32].

Erlotinib and Gefitinib in the First-Line Treatment of EGFR Mutation-Positive NSCLC

Initial phase II trials of erlotinib and gefitinib in the first-line setting demonstrated at best modest efficacy in unselected patients, with rather disappointing response rates (4–23%), PFS (1.6–3.5 months) and OS times (5–13 months) [33–39] (table 1). This was in accordance with results of the large second- and third-line trials BR.21 and ISEL, demonstrating a rather minor clinical benefit of EGFR TKI therapy compared to placebo in a likewise unselected patient population [12, 13]. Subgroup analyses and the discovery of activating *EGFR*

Table 1. Selected studies reporting the activity of first-line erlotinib and gefitinib in NSCLC

Study	Study phase	Population	Treatment (patients, n)	ORR, %	Median PFS/TTP, months	Median OS, months
<i>Patients not selected for TKI sensitivity</i>						
Giaccone [33]	phase II	unselected	erlotinib (53)	22.7	2.8	13
Reck [34]	phase II	unselected	gefitinib (58)	5.0	1.7	7.2
Akerley [35]	phase II	unselected	erlotinib (40)	15	2.0	11.7
Jackman [36]	phase II	elderly	erlotinib (80)	10	3.5	10.9
INVITE [38]	phase II	elderly	gefitinib (97)	3.1	2.7	5.9
			vinorelbine (99)	5.1	2.9	8.0
					HR 1.19; p = 0.31	
Hesketh [37]	phase II	poor PS	erlotinib (76)	8.0	2.1	5.0
Lilenbaum [39]	phase II	poor PS	erlotinib (52)	2.0	1.9	6.5
			Carbo/Pac (51)	12.0	3.5	9.7
					HR 1.45; p = 0.06	
<i>Patients clinically selected for TKI sensitivity</i>						
Niho [44]	phase II	Asian	gefitinib (40)	30	NA	13.9
Yang [43]	phase II	Asian	gefitinib (106)	50.9	5.5	22.4
Ebi [46]	phase II	Asian, elderly	gefitinib (49)	25	4.0	10
West [101]	phase II	BAC	gefitinib (104)	17	4.0	13
Cadranel [102]	phase II	BAC	gefitinib (88)	12.9	2.9	13.2
Lee [103]	phase II	Asian, adenocarcinoma, never-smokers	gefitinib (36)	69	8.2	20.1
Jackman [104]	phase II	female, adenocarcinoma, never-smokers, former-smokers	erlotinib (84)	32	5.6	22.7
IPASS [45]	phase III	Asian, adenocarcinoma, never-smokers, former light-smokers	gefitinib (609)	43.0	5.7	18.8
			Carbo + Pac (608)	32.2	5.8	17.4
				p < 0.001	HR 0.74; p < 0.001	
					p = 0.109	
First-SIGNAL [105]	phase III	Asian, adenocarcinoma, never-smokers	gefitinib (159)	55	5.8	22.3
			Cis + Gem (150)	46	6.4	22.9
				p = 0.101	HR 1.19; p = 0.138	
					p = 0.604	
<i>Patients molecularly selected for TKI sensitivity</i>						
Asahina [106]	phase II	EGFR M+	gefitinib (16)	75	8.9	NA
Inoue [107]	phase II	EGFR M+	gefitinib (16)	75	9.7	NA
Sequist [108]	phase II	EGFR M+	gefitinib (31)	55	9.2	17.5
Rosell [109]	phase II	EGFR M+	erlotinib (217)	70.5	14	27
Inoue [110]	Phase II	EGFR M+, poor PS	gefitinib (30)	66	6.5	17.8
NEJSG002 [48]	phase III	EGFR M+	gefitinib (115)	73.7	10.8	30.5
			Carbo + Pac (115)	30.7	5.4	23.6
				p < 0.001	HR 0.30; p < 0.001	
				62.1	9.2	p = 0.31
WJTOG3405 [50]	phase III	EGFR M+	gefitinib (88)	32.2	6.3	36
			Cis + Doc (89)			39
				p < 0.0001	HR 0.48; p < 0.0001	
				83	13.1	HR 1.18
OPTIMAL [47]	phase III	EGFR M+	erlotinib (82)	36	4.6	NA
			Carbo + Gem (72)			NA
				p < 0.0001	HR 0.16; p < 0.0001	
				58	9.7	p = NS
EURTAC [49]	phase III	EGFR M+	erlotinib (86)	15	5.2	22.9
			Carbo/Cis + Doc/Gem (87)			18.8
				p < 0.0001	HR 0.37; p < 0.0001	
					p = 0.41	

TTP = Time to progression, PS = performance status, BAC = bronchoalveolar carcinoma, EGFR M+ = EGFR mutation-positive, Carbo = carboplatin, Pac = paclitaxel, Cis = cisplatin, Gem = gemcitabine, Doc = docetaxel, NA = not applicable, NS = not significant.

gene mutations as predictors for TKI effectiveness [17, 21, 33, 35, 36] since then yielded a conceptual change in selecting patients for EGFR-targeted therapies. Some of the upcoming trials have used clinical criteria (such as smoking status, sex, histology, and ethnicity) and some have used the *EGFR* mutational status, whereas others have selected patients with potential intolerance to chemotherapy based on poor performance status and higher age. The latter concept, selecting patients who were expected to be intolerant of first-line chemotherapy, did not demonstrate superiority of EGFR TKI over standard of care [37, 39–42]. In contrast, several phase II trials, and in particular the phase III study IPASS, selected patients for clinical surrogate markers (i.e. female patients, Asians, never- or former light-smokers). All of these trials reported an increase in ORR (13–43%) and PFS (4–5.9 months). Additional *EGFR*-mutational analyses revealed that the benefit was consistently highest in patients with tumors harboring the activating *EGFR* gene mutations [36, 43–46] (table 1). These findings eventually stimulated 4 randomized phase III trials comparing first-line erlotinib or gefitinib with cytotoxic chemotherapy in patients with proven *EGFR*-mutant NSCLC. In such molecularly selected populations, the OPTIMAL, WJTOG3405, and NEJSG002 trials in Asian patients and the EURTAC trial in Caucasian patients clearly demonstrated the superiority of erlotinib or gefitinib over platinum doublet chemotherapy – the standard of care – in terms of PFS (OPTIMAL: 13.1 vs. 4.6 months, hazard ratio (HR) 0.16; WJTOG3405: 9.2 vs. 6.3 months, HR 0.48; NEJSG002: 10.8 vs. 5.4 months, HR 0.30; EURTAC: 9.7 vs. 5.2 months, HR 0.37). Also the objective response rate was more than doubled in the EGFR TKI arms (OPTIMAL: 83% vs. 36%; WJTOG3405: 62% vs. 32%; NEJSG002: 74% vs. 31%; EURTAC: 58% vs. 15%) [47–50]. Recently published meta-analyses consistently confirmed that *EGFR* mutations predict response to EGFR TKI with much higher sensitivity (0.78; 95% confidence interval (CI) 0.74–0.82) than do *EGFR* gene copy numbers or EGFR expression levels [51]. First-line treatment with erlotinib or gefitinib in molecularly selected patients increases the chance of obtaining an ORR more than 2-fold (70% vs. 33%) when compared to chemotherapy (relative risk (RR) 2.06; 2p < 0.00001). At the same time, the hazard of progression is reduced by 65% (HR 0.35; 2p < 0.00001) [52]. In *EGFR* mutation-positive patients treated with erlotinib or gefitinib, those with exon 19-deleted tumors appear to have a longer PFS (14.6 vs. 9.7 months) and OS (30.8 vs. 14.8 months) as compared to patients with *EGFR* L858R-mutant tumors [53, 54], although this was not consistently reproducible throughout all trials [48, 50, 55]. The European Medicines Agency (EMA) approved gefitinib in 2009 due to results from the IPASS and INTEREST trials, and erlotinib in 2011 due to EURTAC trial results for the first-line treatment of patients with *EGFR*-mutant NSCLC, but both drugs have yet to be licensed for this indication by the U.S. Food and Drug Administration (FDA). This is in part due to the fact that none of these trials nor the

meta-analysis (HR 0.96, 2p = 0.71) has actually demonstrated a significant improvement in OS for recipients of first-line EGFR TKI therapy [52]. There is evidence, however, that the response rates are higher when TKIs are given upfront to chemotherapy-naïve patients compared to chemotherapy-treated patients [56]. It is highly unlikely that such an overall survival advantage will ever be demonstrated, as nearly all patients with known *EGFR* mutations who receive first-line chemotherapy cross over to TKI treatment. Furthermore, EGFR TKIs are also active in the second-line and maintenance treatment (SATURN, INFORM trial) – especially in *EGFR*-mutant tumors [57, 58]. Anyhow, given that in many trials the HR for OS was slightly in favor of first-line EGFR TKI [52] and that the quality of life was maintained for much longer in TKI-treated patients [59], it is concluded that patients with *EGFR*-mutant tumors gain the greater benefit when TKIs are given early during the natural course of the disease [56]. Especially patients who are older or have a poor performance status will derive a greater benefit from first-line EGFR TKIs [46, 60]. These trials also clearly show that proper selection of patients is absolutely crucial for treatment with EGFR-targeted agents in both directions. First-line EGFR TKIs in patients with unknown or wild-type *EGFR* status were detrimental in terms of PFS and OS as compared to chemotherapy [45, 61, 62]. In line with this, early trials combining EGFR TKIs with first-line chemotherapy in unselected patients (INTACT-1 and -2 trials) did not lead to an increased treatment efficacy [63, 64], but recent trials in selected patients suggest that a combination may work (CALGB 30406 trial) [65].

Afatinib – an Irreversible ErbB Family Blocker

Tumors harboring drug-sensitive EGFR mutations that initially respond to first-generation EGFR TKIs eventually acquire resistance, which is observed after, on average, 9–13 months of treatment [47–50, 66]. This is most likely due to selection of TKI-resistant subclones, which either pre-exist or newly emerge as a result of cancer-inherent genomic instability. Approximately 50% of these cases of acquired resistance to erlotinib or gefitinib harbor the EGFR T790M mutation, which appears to increase the ATP affinity to the level of the wild-type EGFR kinase and thereby closes the ‘therapeutic window’ for ATP-competitive EGFR TKIs [67]. The mutation may be also present in a minor population of EGFR TKI-naïve tumor cells and thus confer primary resistance [68]. Other mechanisms of acquired resistance include small-cell histologic transformation, tumor stroma-mediated effects, or up-regulation of parallel signaling pathways, e.g. via insulin-like growth factor-1 receptor (IGF1R), c-Met, or human epidermal growth factor receptor (HER)2 [69–71]. The latter can augment the mitogenic EGFR signal, and somatic *HER2* mutations or amplifications and HER2 overexpression have been

Table 2. Studies reporting the activity of first-line afatinib in NSCLC

Study	Study phase	Population	Treatment (patients, n)	ORR, %	Median PFS/TTP, months	Median OS, months
LUX-Lung 2 [14]	phase II	EGFR M+	afatinib 50 mg (99) afatinib 40 mg (30)	62 60	12 (13.7 Del19/L858R)	24
LUX-Lung 3 [55] (worldwide)	phase III	EGFR M+	afatinib (230) Cis/Pem (115)	56 (61 Del19/L858R) 23 (22 Del19/L858R) $p < 0.0001$	11.1 (13.6 Del19/L858R) 6.9 (6.9 Del19/L858R) HR 0.58; $p = 0.0004$	NA
LUX-Lung 6 (Asia)	phase III	EGFR M+	afatinib 40 mg Cis/Gem (330 planned)	observation period; results pending	still recruiting	still recruiting

TTP = Time to progression, EGFR M+ = EGFR mutation positive, Cis = cisplatin, Pem = pemetrexed, Gem = gemcitabine, NA = not applicable.

detected in about 2%, 2–10%, and 40% of lung adenocarcinomas, respectively [72, 73]. Furthermore, a compensatory shift in the phosphorylation-dephosphorylation equilibrium of HER3, which itself lacks kinase activity but forms heterodimers with other ErbB family members, can induce resistance to first-generation EGFR TKIs [74]. This provides a strong rationale for a combined EGFR/HER2/HER3 blockade. Against this background, the orally available TKI afatinib has been developed, which covalently binds the RTK domains and equipotently inhibits EGFR, HER2 and HER4 and the transphosphorylation of HER3. The *in vivo* activity of afatinib against T790M-mutant NSCLC has not been shown so far; however, the inhibitor has proven *in vitro* activity against lung cancer cells with the EGFR T790M mutation, and also against cells with additional resistance mutations such as EGFR T854A and the variant III deletion (EGFRvIII) [75, 76]. The LUX-Lung 2 trial explored the 40 and 50 mg once-daily dosage in TKI-naïve patients and showed equal efficacy [14]. In the situation of acquired resistance, i.e. in TKI-pretreated patients, a higher dosage is needed, as indicated by *in vitro* data [76]. In this situation, the recommended starting dosage is 50 mg once a day, as used in the LUX-Lung 1 and 4 trials [77, 78]. The LUX-Lung 1 phase IIB/III trial investigated afatinib versus placebo in NSCLC patients who were progressing after prior treatment with at least 1 line of platinum-based chemotherapy and erlotinib or gefitinib. Patients were clinically enriched by enrolling only those who derived a minimum of 12 weeks of disease control under a first-generation EGFR TKI. However, afatinib did not meet the primary endpoint of extending OS compared to placebo (10.8 vs. 12 months, HR 1.08, 95% CI 0.86–1.35), presumably due to subsequent therapies; PFS was (though in both groups rather mean in this clinical situation) in favor of afatinib (3.3 vs. 1.1 months, HR 0.38; $p < 0.0001$), with some improvement in cancer-related symptoms [77]. The LUX-Lung 2 trial, a phase II study, narrowed the study population to patients with advanced NSCLC (stage IIB with pleural effusion and stage IV) harboring activating *EGFR* gene mutations who had 0 or 1 line of prior chemotherapy but were naïve for EGFR TKIs. The overall response rates were similar with once-daily dosing of 40 or 50 mg afatinib (60% for 40 mg vs. 62% for 50 mg), but more side effects

were observed in the group receiving 50 mg [14]. Based on these findings, LUX-Lung 3, the so far largest registrational phase III trial in *EGFR* mutation-positive adenocarcinoma (345 patients randomized), randomized 40 mg once daily of afatinib versus a highly effective and tolerable combination chemotherapy consisting of cisplatin and pemetrexed. The trial was conducted throughout Asia, Europe, North/South America, and Australia, with 72% of enrolled patients having Asian ethnicity and 28% being non-Asians. Treatment with afatinib led to a prolonged PFS (11.1 vs. 6.9 months, HR 0.58, 95% CI 0.43–0.78) compared to cisplatin/pemetrexed and a significantly higher ORR (56% vs. 23%; $p < 0.0001$), as assessed by independent review [79, 80]. The superiority of afatinib was consistent in all relevant subgroups. In those 308 patients with common *EGFR* mutations (i.e. exon 19 deletion or *EGFR* L858R) the median PFS even reached 13.6 months with afatinib versus 6.9 months with chemotherapy (HR 0.47, 95% CI 0.34–0.65) (tables 1 and 2). As with erlotinib and gefitinib, patients with *EGFR* exon 19-deleted tumors appeared to have a greater benefit from afatinib (HR 0.28, 95% CI 0.18–0.44) than patients with *EGFR* L858R-mutant tumors (HR 0.73, 95% CI 0.46–1.17). The afatinib group furthermore demonstrated a significant delay in time to deterioration of cancer-related symptoms such as cough (HR 0.6; $p = 0.007$) and dyspnea (HR 0.68; $p = 0.015$) and increased quality of life [55]. OS data have yet to be reported. Currently recruiting trials compare afatinib in the first line against cisplatin/gemcitabine (LUX-Lung 6) in Asian patients, and head-to-head against gefitinib in the first-line treatment (LUX-Lung 7, phase IIB) of *EGFR* mutation-positive NSCLC, and with erlotinib in the second-line treatment (LUX-Lung 8, phase III) of NSCLC patients with squamous histology.

Adverse Events Related to First-Line Treatment with EGFR TKIs and ErbB Family Blockers

EGFR-targeting agents are generally associated with less serious toxicities than traditional anti-neoplastic agents. The latter confer the risk of organ toxicities, severe myelosuppression, and neutropenic sepsis, with treatment-related fatal

Table 3. Reported incidences of common side effects of first-line EGFR TKIs in NSCLC (only phase III trials)

Drug	Rash and acne (grade ≥ 3)	Diarrhea (grade ≥ 3)	Fatigue (grade ≥ 3)	Paronychia
Afatinib 40/50 mg	89 (16)	95 (14)	18 (1)	57 (11)
Erlotinib 150 mg	73–80 (2–13)	25–57 (1–5)	5–57 (0–6)	4 (0)
Gefitinib 250/500 mg	66–85 (2–5)	34–54 (1–4)	11–39 (2–3)	14–32 (1)

events in up to 8% of patients, especially if the performance status is poor [81]. Fatal events during EGFR TKI treatment have been rarely reported; they were mainly associated with lung or liver toxicity [14, 48, 82, 83]. Nevertheless, side effects can be severe and may substantially impair the quality of life. The most common adverse events leading to TKI dose reductions are cutaneous reactions (acneiform ‘rash’), paronychia, and diarrhea, because of the abundance of EGFR in skin and mucosa. In a recent published meta-analysis, the appearance of skin rash has been confirmed as an independent predictive factor for survival (HR 0.30; $p < 0.00001$) and tumor progression (HR 0.50; $p < 0.00001$) during erlotinib and gefitinib treatment [84]. In first-line NSCLC trials of erlotinib and gefitinib, most patients developed rash of grades 1 or 2. Only a few patients experienced grade 3 rash (erlotinib: 67%, 2–13% grade ≥ 3 ; gefitinib: 66%, 3% grade ≥ 3) (table 3). Skin reactions normally appear after 1 week and reach maximum severity following 2–3 weeks of TKI treatment, after which they gradually and spontaneously disappear. Therefore, early clinical monitoring and intervention are mandatory to prevent serious complications. In this context, many reviews and treatment consensus papers have dealt with the question of how to cope with EGFR TKI-induced cutaneous reactions [85, 86]. Diarrhea also affects a substantial part of EGFR TKI-treated patients. It is thought to result from excess chloride secretion (‘secretory diarrhea’), which can lead to dehydration, electrolyte imbalances, renal insufficiency, and malnutrition [86]. As diarrhea is a common side effect of conventional cancer treatment regimens, management in the oncology setting is much better established compared to the management of skin-related events [87, 88]. In first-line NSCLC trials, the diarrhea incidence was reported as high as 52% (5% grade ≥ 3) for erlotinib and 47% (4% grade ≥ 3) for gefitinib [47–50]. A much less frequent, yet potentially lethal (30–50% lethality) side effect of EGFR TKIs is interstitial lung disease (ILD), which in general occurs during the first 3 months of treatment (median 24–42 days) in $< 1\%$ of all patients, with higher risk in Japanese populations (1.6–3.5%) [82]. Pre-existing pulmonary fibrosis, prior thoracic irradiation, and smoking history have been identified as further risk factors for developing ILD and should be taken into account when considering a patient for first-line EGFR TKI treatment [89]. Other, mostly reversible side effects include fatigue, nausea/vomiting, and increased liver enzyme levels [45, 49, 50, 55]. Overall, for the ErbB family blockers afatinib and dacomitinib, a similar adverse event profile has been reported as for TKIs [55, 78, 90]. However, although the LUX-Lung 3 trial reported a median PFS of 13.6 months in patients with common mutations, this seems

to have come at the cost of an increased rate of rash (89%, 7–22% grade ≥ 3) and diarrhea (95%, 14.4% grade ≥ 3). This safety profile seems to be a class effect of irreversible ErbB family blockers [91]. Nevertheless, both the diarrhea and rash were manageable and, in LUX-Lung 3, the rate of afatinib discontinuation was low (8% vs. 12% in chemotherapy-treated patients). Importantly, patients on afatinib reported better quality of life, measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) C-30, compared to those on chemotherapy [55].

Conclusions, Clinical Recommendations, and Future Developments

EGFR mutation-positive lung adenocarcinoma has emerged as a distinct subtype of lung cancer with respect to pathogenesis, prognosis, and treatment. In metastatic disease, erlotinib, gefitinib and, recently with the LUX-Lung 3 results, afatinib have been clinically validated as the most effective first-line agents for this tumor entity when compared to platinum-based chemotherapy. Activating *EGFR* gene mutations are the best predictors for EGFR TKI effectiveness; thus, *EGFR*-mutational testing to guide treatment is justified in all patients with newly diagnosed metastatic pulmonary adenocarcinoma. Despite the fact that certain clinical determinants (e.g. never-smoking status, female sex, adenocarcinoma histology, Asian descent) are predictive of such mutations, general genetic testing is recommended to not withhold a superior therapy to patients with *EGFR*-mutant tumors not matching these clinical parameters. Contrariwise, EGFR TKIs may be even deleterious if given to patients with EGFR wild-type tumors [45]. Anyhow, despite its impressive superiority in terms of remission rates and PFS, no OS benefit of first-line EGFR TKI treatment over chemotherapy has been shown, neither in current phase III trials [48, 92] nor in meta-analyses [52]. This is most likely explained by confounding due to post-progression crossover of patients with *EGFR*-mutant tumors to second-line EGFR TKI treatment.

In general, small-molecule EGFR inhibitors are better tolerated than chemotherapy. Side effects like rash and diarrhea are manageable in the outpatient setting under close surveillance, in particular during the first weeks of treatment [86]. With the ErbB family blocker afatinib, patients experienced numerically more diarrhea and skin-related side effects compared to reports from studies using gefitinib or erlotinib. However, the quality of life of afatinib-treated patients was

significantly better than that of chemotherapy-treated patients, which is in accordance with trials with erlotinib and gefitinib. Correspondingly, the discontinuation rate with afatinib was low [55]. Proactive and early treatment of adverse events for ErbB family blockers, including the use of skin moisturizers and sunscreen, sufficient fluid intake, and preemptive prescription of loperamide, as well as effective afatinib dose reduction schemes can efficiently help to maintain patients on treatment, thus increasing the quality of life and allowing the patients to obtain the maximum therapeutic benefit from this agent [93, 94]. Head-to-head comparisons of afatinib with the established agents (LUX-Lung 7 and 8, both currently recruiting) will show whether afatinib – in parallel to the convincing clinical data with second-generation Bcr-Abl kinase inhibitors in the field of chronic myeloid leukemia (CML) [95] – has indeed better antitumor activity than first-generation TKIs. These trials will also help to define the best balance between activity and tolerability.

If not given upfront, all patients with *EGFR* mutation-positive lung adenocarcinoma must be offered an *EGFR* TKI latest during the further course of the disease, with ErbB family blockers as an improved treatment option in the future.

For patients with *EGFR* wild-type tumors or with unknown *EGFR* status, platinum-based combination chemotherapy remains the standard of care [45, 61]. The long-term benefit of treatment with *EGFR* TKIs is limited by acquired resistance, and also primary resistance is encountered. Thus, future concepts like *EGFR* T790M mutant-selective kinase inhibitors [96] or combinatorial drug regimes – i.e. *EGFR* TKI plus c-Met inhibitors [97], *EGFR* TKI plus cetuximab [98] – are urgently needed and currently tested to prevent or overcome resistance against both *EGFR* TKIs and irreversible ErbB family blockers. In the future, this may help to transform advanced lung cancer from a terminal disease to a chronic illness to be managed over years [99, 100].

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