CLINICAL INVESTIGATION

Irreversible EGFR inhibitors in advanced non-small-cell lung carcinoma: rationale and clinical evidence

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The EGFR has become an important target in lung cancer treatment. Reversible inhibitors of this receptor have been shown to improve outcomes for patients whose tumors harbor EGFR mutations, as well as for those with wild-type EGFR. The development of resistance (either primary or acquired) to EGFR tyrosine kinase inhibitors is a common occurrence and irreversible EGFR inhibitors have been developed to overcome this problem. There are now emerging clinical data for the two major irreversible inhibitors; afatinib and dacomitinib. The question of how and when we use these irreversible inhibitors still needs to be answered.

Keywords: afatinib • dacomitinib • erlotinib • gefitinib • irreversible EGFR • non-small-cell lung cancer

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Lung cancer remains a key health issue globally, accounting for the largest estimated number of cancer deaths in men and second largest in women, worldwide [1]. Non-small-cell lung carcinoma (NSCLC) accounts for approximately 85% of all lung cancers diagnosed, which includes three main histological subtypes – adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma [2]. The majority of patients are diagnosed with Stage IV (metastatic) disease and the initial treatment of such patients has largely involved the use of palliative chemotherapy. Despite evidence demonstrating a survival advantage with chemotherapy, the 5-year survival for patients with Stage IV disease remains very poor [3]. The small gains made with chemotherapy prompted a search for new treatment approaches and in the past decade the EGFR has emerged as one of the most important targets for drug development in oncology and specifically in NSCLC [4].

The EGFR (HER-1, ErbB-1) is a transmembrane receptor belonging to the HER family of receptor tyrosine kinases, which also includes HER-2, HER-3 and HER-4 [5]. When the EGFR is activated through binding of a receptor-specific ligand on the cell surface, the receptor forms a dimer that stimulates autophosphorylation through tyrosine kinase activity. This triggers a number of complex and critical intracellular pathways that may lead to cell growth and proliferation, inhibition of apoptosis, facilitation of invasion and metastasis and promotion of tumor-induced angiogenesis [6].

EGFR is overexpressed in 40–80% of NSCLC and its expression is correlated with a poorer clinical prognosis [7]. This, along with its apparent critical role in cancer cell proliferation and survival, meant that the EGFR became an attractive target for drug development in NSCLC. Strategies aimed at inhibition of the activity of the EGFR, using either a monoclonal antibody directed against EGFR or small-molecule inhibitors of the tyrosine kinase domain of EGFR, began a new era of treatment of NSCLC [8]. This review will focus on EGFR tyrosine kinase inhibitors (TKIs) and discuss the evidence and rationale for the development and further testing of irreversible EGFR TKIs.

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Current evidence for the reversible (first-generation) EGFR TKIs

The EGFR-specific TKIs, gefitinib and erlotinib, are now well recognized as therapeutic agents for the treatment of NSCLC. These drugs are orally available small molecules that reversibly bind to the intracellular portion of the EGFR within the tyrosine kinase domain, generally by competing with ATP and inhibiting receptor autophosphorylation and subsequent downstream signaling pathways [6].

Gefitinib was the first EGFR TKI approved for use in NSCLC in the USA after two Phase II studies demonstrated response rates of approximately 10–20% in patients who had received prior chemotherapy [9,10]. Erlotinib was proven to have a similar response rate (12.3%) in a Phase II study [11], and the pivotal NCIC BR.21 trial provided the first Phase III evidence that an EGFR TKI could produce a survival benefit [12]. In this placebo-controlled, double-blinded study, patients who had failed first- or second-line chemotherapy for NSCLC were randomized (2:1) to erlotinib, at a dose of 150 mg daily or placebo. The response rate in the erlotinib arm was 8.9% and there was a statistically significant overall survival (OS) advantage. The median OS in the erlotinib group was 6.7 versus 4.7 months in the placebo group (hazard ratio [HR]: 0.70; $p < 0.001$).

Perhaps surprisingly, a Phase III trial of gefitinib did not demonstrate an equivalent benefit. In the ISEL study, gefitinib at 250 mg daily was compared with placebo as a second- or third-line treatment in patients with NSCLC who were refractory to or intolerant of their most recent chemotherapy regimen [13]. The median survival did not differ significantly in each arm – 5.6 months for those receiving gefitinib versus 5.1 months for those that received placebo. Preplanned subgroup analyses did demonstrate a significant survival benefit for those patients who were never smokers and those patients of Asian background. Female patients and patients with adenocarcinoma had higher response rates. Higher response rates in all these subgroups were also seen in the NCIC BR.21 trial [12].

Phase III trials combining gefitinib or erlotinib with commonly used platinum-doublet chemotherapy regimens as first-line therapy were also disappointing. Two trials combining gefitinib with chemotherapy (cisplatin/gemcitabine in INTACT 1 and carboplatin/paclitaxel in INTACT 2) and two trials combining erlotinib with chemotherapy (cisplatin/gemcitabine in TALENT and carboplatin/paclitaxel in TRIBUTE) demonstrated no additional benefit for those patients receiving an EGFR TKI in combination with chemotherapy over chemotherapy alone [14–17]. The median survival in all arms of these studies ranged from 8.7 to 10.9 months. In the TRIBUTE study there appeared to be a benefit in patients who had never smoked. Never smokers had a median survival of 22.5 months [16]. The reasons for the lack of benefit are not clear, but possibilities include a mechanistic interaction of EGFR TKIs with cell-cycle arrest, resulting in chemotherapy resistance; pharmacokinetic interactions (though no evidence for this was detected); or the lack of efficacy of a triplet compared with a doublet, as seen in chemotherapy containing triplets.

It had become apparent that only a subset of patients with NSCLC had EGFR-pathway dependent disease. Predictors of response included female sex, Asian ethnicity, absence of smoking history and adenocarcinoma histology [8]. It also became evident that these clinical characteristics were associated with mutations within the tumor of the tyrosine kinase domain of the EGFR [18]. In Caucasian patients, EGFR mutations are present in approximately 10% of NSCLC cases but 30–50% of tumors from patients of East Asian background, particularly non-smokers, have mutations [19]. Perhaps more important than this association, was the mounting retrospective data identifying a link between response to an EGFR TKI and the presence of an EGFR mutation, with retrospective response rates between 30 and 100% [4]. The IPASS, which included Asian patients with adenocarcinoma who were lifelong non-smokers or light ex-smokers, compared gefitinib with chemotherapy as first-line therapy and confirmed prospectively that patients with EGFR-mutated NSCLC treated with an EGFR TKI had higher response rates and longer progression-free survival than those patient without mutations. In a preplanned subgroup analysis of 261 patients with EGFR-mutated tumors, there was significant difference in progression-free survival (PFS) attained with gefitinib versus carboplatin and paclitaxel (9.5 vs 6.3 months; HR: 0.48; $p < 0.001$). The objective response rate (ORR) to gefitinib in patients harboring EGFR mutations was 71.2%. In contrast, patients without EGFR mutations had improved PFS with chemotherapy rather than gefitinib [20].

The mutations in the *EGFR* are most commonly in-frame deletions of exon 19 (~45–50%) and the L858R point mutation in exon 21 (~40–45%) [21]. These mutations are oncogenic – that is they promote survival and inhibit apoptosis by constitutively activating the EGFR-signaling pathway [21]. These 'activating' mutations confer a dependence on the mutated kinase for survival of the tumor cells and treatment of such cells with EGFR TKIs blocks these downstream signals leading to a predominance of apoptotic signals, which clinically translates into a reduction in tumor size [19].

Mechanisms of resistance to EGFR TKIs

Most patients with NSCLC that harbor an EGFR mutation, respond to initial monotherapy with an EGFR TKI [22]. Despite the striking efficacy at the outset, the majority of patients experience disease progression within approximately 12 months of treatment [23]. The reason for this in many patients is the development of acquired resistance [22,24]. Understanding these mechanisms of resistance is important, as it facilitates the development of new therapies such as the irreversible EGFR TKIs.

Primary resistance

There is a subset of patients who are refractory to initial therapy and have so called primary resistance. For example, insertion mutations in exon 20 of the *EGFR* gene appear to render the receptor less sensitive to EGFR TKIs compared with other *EGFR* mutations [25]. *KRAS* mutations are also present in 15–30% of NSCLCs and there is strong evidence that the presence of a *KRAS* mutation within a tumor predicts for negative response to single-agent EGFR TKIs in patients with advanced NSCLC (and other tumor types) [21,26]. However, mutations in the *KRAS* oncogene appear, in general, to be mutually exclusive with EGFR mutations and, therefore, whether poor responses to EGFR TKIs in *KRAS*-mutated patients is due to the presence of mutated *KRAS* or the absence of mutated EGFR is difficult to ascertain [21].

Acquired resistance

The relatively short-lived responses to EGFR TKIs in patients with EGFR-mutated NSCLC are thought to be due to the development of acquired resistance, for which there may be multiple underlying mechanisms. One of the most common mechanisms for acquired resistance is the development of an additional mutation in EGFR. The best recognized mutation of this type is at exon 20 involving the substitution of methionine for threonine at position 790 (T790M) [27]. This mutation causes a change in the structure of the tyrosine kinase domain and hinders erlotinib and gefitinib from binding to EGFR [6]. Although the T790M mutation has been associated with acquired resistance, there is evidence that it is present in some patients prior to exposure to an EGFR TKI, which may explain development of resistance in these patients as cell lines with this mutation may be selected out during therapy with an EGFR TKI [28]. There is also some data to suggest that amplification of the *c-MET* proto-oncogene is a culprit for development of acquired resistance to EGFR TKIs [29]. This amplification leads to EGFR-independent activation of the PI3K–AKT pathway through activation of HER-3-dependent signaling [22]. The combination of EGFR T790M mutations and MET amplification account for approximately 60–70% of all known causes of acquired resistance [22]. Other mechanisms of resistance include downregulation of the PTEN pathway and epithelial to mesenchymal transition, which allows reduced reliance on EGFR [24].

Irreversible EGFR inhibitors

The irreversible EGFR inhibitors differ chemically from the reversible inhibitors, as they contain a reactive Michael-acceptor group that forms a covalent bond with the receptor tyrosine kinase domain, specifically at Cys-797 [30]. This allows a permanent attachment to the tyrosine kinase domain, whereas the reversible TKIs exhibit nonpermanent binding. By attaching to the receptor in this way the irreversible EGFR TKIs can overcome the resistance conferred by T790M [31]. This holds much importance because, as mentioned previously, this mutation is one of the most common forms of acquired resistance to reversible EGFR TKIs and so these drugs provide further therapeutic options for patients with NSCLC in this predicament. There is a number of irreversible EGFR inhibitors that have been, or are being tested in Phase I–III clinical trials, including neratinib (HKI-272) and the more promising dacomitinib (PF299804) and afatinib (BIBW 2992). EKB-569 [32] and CI-1033 [33,34] have also been tested in patients with NSCLC, but they are not included in this review and no further large studies using these agents in NSCLC are planned.

Neratinib (HKI-272)

Neratinib is an orally administered, irreversible inhibitor of the tyrosine kinase HER family (EGFR, HER-2 and HER-4) [35]. It targets a conserved cysteine residue (Cys-797, also known as Cys-773) within the catalytic cleft of the HER family [36]. Neratinib has been tested in a Phase I trial of 72 patients with advanced solid tumors [36]. Most patients in the study had been heavily pretreated, with 34% having four or more previous cytotoxic therapy regimens. Among the 14 patients with NSCLC, six (43%) showed stable disease after ≥24 weeks. Of note, all patients with stable disease had previously failed erlotinib or gefitinib. Grade 3 diarrhea was the dose-limiting toxicity and the maximum tolerated dose was 320 mg. Grade 3 or higher neratinib-related adverse events occurred in 39% of patients and they were mostly gastrointestinal in nature (diarrhea: 32%; fatigue: 4%; vomiting: 4%). Rash was much less frequent than with erlotinib or gefitinib.

However, further evaluation in a Phase II study proved disappointing [37]. This study included 172 patients with advanced NSCLC. Most patients had progressed on erlotinib or gefitinib but 28 were TKI

naive. The patients were split into three arms. Those that had received ≥12 weeks of TKI therapy were placed in arm A if they were EGFR-mutation positive (91 patients) and arm B if they were EGFR wild-type (48 patients). Arm C included those that were EGFR TKI naive with adenocarcinoma and a light smoking history (28 patients). On enrollment, patients were initially treated with 320 mg but this dose was later reduced to 240 mg because of dose delays and reductions mostly associated with diarrhea. Of the 158 evaluable patients, only three patients had a partial response (all in arm A) and 14 had stable disease for ≥ six cycles. The median PFS time was 15.3, 16.1 and 9.3 weeks in arms A, B and C, respectively. The three patients who had a partial response had point mutations in exon 18 G719X. The total number of patients with this mutation was four and the median PFS for them was 52.7 weeks. No patients with a T790M mutation responded to neratinib. As a result of these data there are no further trials testing neratinib in NSCLC.

Dacomitinib (PF299804)

Dacomitinib is a potent, orally available, pan-HER inhibitor (EGFR, HER-2 and HER-4) [38,39]. Dacomitinib has been associated with anticancer activity in gefitinib- and erlotinib-sensitive and -resistant preclinical NSCLC models [40]. In a Phase I study of 121 patients (47% NSCLC) with advanced solid tumors, two dosing schedules (continuous and intermittent) were used with doses between 0.5 and 60 mg/day [38]. The most common toxicity was diarrhea and the maximum tolerated dose was 45 mg/day. Of the patients with NSCLC there were four partial responses and 28 patients with stable disease after ≥6 weeks. The four patients who had a partial response had been previously treated with erlotinib or gefitinib. In terms of the EGFR mutation status in the responders, two had exon 19 deletions, one had an exon 20 insertion and one patient had unknown mutational status. There were four patients who had a T790M mutation and none of them had a response to treatment.

Dacomitinib has been evaluated in a number of Phase I and II studies in patients with NSCLC who had previously been treated with an EGFR TKI. A Phase I study that enrolled 44 patients, among the 29 evaluable, two patients had a partial response and eight had stable disease [41]. It was not a requirement to have been treated with an EGFR TKI to be enrolled but most patients in this trial had received prior EGFR inhibitors (94%) and prior chemotherapy (79%). Again, the maximum tolerated dose was 45 mg and the most frequently reported toxicity was diarrhea (78%) and rash (65%). Both partial responders had received three or more lines of chemotherapy. One patient had received gefitinib previously, the other erlotinib. In a Phase I/II trial of patients who had progressed following one to two lines of chemotherapy and erlotinib, 66 patients were enrolled and 41 were evaluable, 36 of whom had adenocarcinoma [42]. A total of 67% of patients with adenocarcinoma had a response or stable disease versus 40% of patients with nonadenocarcinoma. The most common toxicity was diarrhea (82%) and the levels of grade 3 toxicities were acceptable – skin (14%), diarrhea (10%) and fatigue (10%). Of note, three patients had a grade 4 pulmonary embolus, but this was in the setting of progressive disease. A Phase I/II trial of Korean patients who had previous platinum-based chemotherapy and erlotinib or gefitinib is ongoing [43]. Preliminary data in 30 patients have demonstrated an ORR of 8% and 20% had partial responses or stable disease for >24 weeks. The PFS at 4 months was 35% and OS at 6 months was 87%. There was no change in health-related quality of life scores and grade 3 diarrhea (4%) and rash (4%) were not frequent. All patients enrolled were *KRAS* wild-type. A comparable Phase II study, also enrolling *KRAS* wild-type patients, has reported preliminary data from 62 patients [44]. This was an open-label study of 45 mg of dacomitinib in patients who had failed ≥ one chemotherapy regimen and erlotinib. In this study, three patients had a partial response and 35 had stable disease after ≥6 weeks. In total, 86% of patients had diarrhea and 46% had a rash. There was also a decline in patient-reported cough, dyspnea and chest pain.

Dacomitinib has also been tested in patients with NSCLC who are EGFR TKI naive. A global, multicenter, randomized Phase II study compared dacomitinib (45 mg daily) with erlotinib (150 mg daily) in patients with advanced NSCLC who had failed one or two chemotherapy regimens [45]. Patients who had received an EGFR TKI previously were excluded and patients had to have tumor tissue available for molecular testing. The primary end point was PFS. In total, 188 patients were recruited over a 12-month period. Most patients were male (59%) and had good performance status. Amongst the 65% of patients that had adenocarcinoma, 25% were of east Asian background, 21% were non-smokers and 16% were positive for EGFR mutations. A third of patients had received at least two lines of chemotherapy. There was a longer median PFS (12.4 vs 8.3 months; HR: 0.681; p = 0.019) in the dacomitinib arm compared with the erlotinib arm. The objective response rate was also higher in the dacomitinib arm (17.0 vs 4.3%). One patient receiving dacomitinib had a complete response. There was some imbalance between the baseline characteristics of the

patients in each arm with more ECOG 2 (19.1 vs 3.2%) and more EGFR-mutation positive patients (20.2 vs 11.7%) in the dacomitinib arm. In terms of toxicity, diarrhea (71 vs 48%) and acne (53 vs 34%) were more common in patients receiving dacomitinib.

Dacomitinib is also being tested as a first-line therapy in patients with EGFR mutations in a Phase II trial given the Phase III evidence proving the efficacy of gefitinib in this setting [46]. Preliminary results from the 29 evaluable patients include one complete response, six partial responses and 16 patients with stable disease after ≥6 weeks. PFS at 3, 4 and 6 months was 90, 79 and 79%, respectively.

■ Afatinib (BIBW 2992)

Afatinib is a potent, oral irreversible EGFR, HER-2 and HER-4 inhibitor. It covalently binds to Cys-773 of EGFR and Cys-805 of HER-2 [47]. There has been a number of Phase I trials testing afatinib as monotherapy in patients with advanced solid malignancies [48–50]. Doses were between 10 and 65 mg and diarrhea and rash were common side effects. The dose-limiting toxicities included diarrhea, rash, mucositis and dyspnea secondary to reversible pneumonitis (one case). In one trial, three patients with NSCLC (two with in-frame deletion mutations in exon 19 of *EGFR*) experienced confirmed partial responses sustained for 24, 18 and 34 months, respectively [49]. A fourth patient in the same trial with NSCLC had a nonconfirmed partial response.

The Phase I component of LUX-Lung 4 has also been reported, in which Japanese patients with NSCLC were treated with afatinib after failure of a prior platinum-doublet chemotherapy and/or a reversible TKI [51]. Patients received 20–50 mg of afatinib daily and the one dose-limiting toxicity was observed at 50 mg/day (grade 3 mucositis). The most frequent drug-related adverse events were diarrhea, dry skin, stomatitis, rash, paronychia and anorexia. Six out of 12 patients had tumor-size reductions and durable stable disease was achieved in three patients, including one with *EGFR* exon 19 and T790M mutations. The recommended dose for the Phase II component of LUX-LUNG 4 was 50 mg and the results have been recently reported [52]. In total, 62 patients with advanced NSCLC were enrolled, most were female (77%) and had never smoked (69%). In total, 73% of patients were EGFR-mutation positive. Most had received prior TKI therapy (11% erlotinib, 79% gefitinib and 10% both) and 65% of patients had a response to the first-line EGFR TKI. Upon independent assessment, 8.2% of patients had a partial response and 67% had disease control for at least 8 weeks. The median duration of response to afatinib was 12.0 months. The median PFS was 4.6 months and the median OS was 19.0 months. Two patients had primary tumor T790M mutations, one of whom had a long stable disease period (308 days). Grade 3 diarrhea and grade 3 rash occurred in 24 and 25% of patients, respectively.

A larger Phase IIB/III study (LUX-Lung 1) also assessed afatinib as monotherapy in a similar cohort of patients [53]. In this double-blinded, randomized study, 585 patients with stage IIIB/IV adenocarcinoma of the lung either received placebo or afatinib (50 mg daily) after failure of one to two lines of chemotherapy and progression following ≥12 weeks of erlotinib or gefitinib. The primary end point was OS and secondary end points included PFS and ORR. There was no prospective EGFR mutation testing. A total of 58% of patients were of Asian ethnicity and 60% were female. A total of 81% had a reversible TKI for ≥24 weeks, 45% having responded to prior treatment. Median overall survival for patients receiving afatinib was 10.78 versus 11.96 months for patients receiving placebo (HR: 1.08; 95% CI: 0.86–1.35), and thus the primary end point was not met. Afatinib was, however, superior to placebo upon analysis of the PFS and ORR. The median PFS was 3.3 months in the afatinib arm versus 1.1 months in the placebo arm (HR: 0.38; $p < 0.001$) and ORR (independent assessment) were 7.4% for afatinib versus 0.5% for placebo. The PFS benefit was clinically meaningful, with improvement in lung-cancer related symptoms of cough, dyspnea and pain. Reasons for the lack of survival benefit in this study may include a greater proportion of patients in the placebo group going on to have both chemotherapy and an EGFR TKI after disease progression [47]. Despite the lack of improvement in OS, this trial demonstrates the significant clinical activity of afatinib in a refractory population of EGFR-TKI pretreated NSCLC patients.

The role of afatinib as a first-line EGFR TKI has been explored (LUX-Lung 2) and preliminary results have been reported [54]. This open-label Phase II study included patients with stage IIIB/IV adenocarcinoma of the lung who were proven to have activating *EGFR* mutations (exons 18–21) by direct sequencing. Patients had no previous TKI therapy but could either be chemotherapy naive or have progressed after one line of chemotherapy. A dose of 40 or 50 mg/day was used. A total of 444 patients were screened for EGFR mutations and 129 received treatment. L858R mutation was seen in 54 (42%), del19 in 52 (40%) and other mutations in 23 (18%) patients. Analysis revealed an ORR and disease control rate of 62 and 94%, respectively, for del19; 52 and 85%, respectively, for L858R; and 43 and 78%, respectively, for other mutations based on investigator assessment. The median PFS was estimated to be 12 months for the overall group.

Almost all patients (95%) had diarrhea and rash and these reached grade 3 in 18 and 19% of cases, respectively. However, amongst those patients treated at the lower dose of 40 mg daily, the rate of grade 3 diarrhea was approximately 7%. These results are comparable to first-line TKIs [55] and provides the rationale for Phase III testing.

In Phase I trials, afatinib has also been combined with chemotherapy in patients with advanced solid malignancies and appeared to be well tolerated in this setting [56–58]. One trial enrolled nine patients with NSCLC who received afatinib (20–50 mg) in combination with weekly paclitaxel [56]. In total, 77% of patients had adenocarcinoma and three patients were non-smokers. Durable partial responses were achieved in three patients and a further four patients had stable disease. The most frequent adverse events were fatigue, rash and diarrhea. Two patients needed a dose reduction of afatinib.

Ongoing trials

The ideal place for irreversible EGFR TKIs in the treatment of advanced NSCLC is yet to be determined, but there are many ongoing trials attempting to answer this question. One particular area of interest is the potential ability of irreversible EGFR TKIs to overcome acquired resistance to gefitinib or erlotinib. Failure of the first-line reversible EGFR TKIs often leaves patients with no further treatment options. There are preclinical data to suggest that drugs such as afatinib and dacomitinib may have a role in overcoming resistance to reversible EGFR inhibitors. Both of these drugs have shown efficacy in tumor cells harboring the T790M mutation [31,59]. Preliminary results from a Phase I study combining afatinib and cetuximab after failure of erlotinib or gefitinib (in patients with activating EGFR mutations) have demonstrated activity in patients with T790M-mutated tumors [60]. Of 13 evaluable patients with T790M mutations, four had a partial response to treatment with afatinib and cetuximab. Dacomitinib is also being evaluated after the failure of prior EGFR TKI therapy. The BR.26 trial (NCT01000025) is a Phase III study comparing dacomitinib with placebo in patients with stage IIIB/IV NSCLC after failure of chemotherapy and at least one of gefitinib or erlotinib [101].

The irreversible TKIs may also have a role as treatment for patients who have not previously been exposed to an EGFR TKI, either in the setting of wild-type EGFR or in the presence of EGFR mutations. This class of drugs may improve on the results of gefitinib and erlotinib in the first-line setting due to their ability to covalently bind to the tyrosine kinase domain of the EGFR and hence their potential for superior potency [61]. The ARCHER 1009 study (NCT01360554) is a Phase III study looking at the question of whether dacomitinib is superior to erlotinib as the first exposure to EGFR-targeted therapy in patients with advanced NSCLC who have progressed after chemotherapy [101]. A Phase II study comparing afatinib with gefitinib (NCT01466660) as first-line therapy in patients with EGFR-mutated patients will soon be opening and should provide further evidence in this area [101]. LUX-Lung 3 (NCT00949650) and LUX-Lung 6 (NCT01121393) are also looking at their use in the first-line setting, but these trials are comparing afatinib with standard first-line chemotherapy (cisplatin/pemetrexed in LUX-Lung 3 and cisplatin/gemcitabine in LUX-Lung 6) in patients with advanced adenocarcinoma of the lung harboring EGFR mutations [101]. These studies may also identify whether specific EGFR mutations are more likely to respond to irreversible TKIs.

Combining the irreversible TKIs with other agents is also an attractive therapeutic option. As described above, afatinib has been coadministered safely with chemotherapy in a number of Phase I studies. LUX-Lung 5 (NCT01085136), a Phase III study combining afatinib with paclitaxel after failure of afatinib monotherapy, previous erlotinib or gefitinib and chemotherapy, will look at this further [101]. Combining irreversible TKIs with targets downstream for the EGFR is also being evaluated. Phase I studies combining dacomitinib with a C-MET inhibitor (NCT01121575) and afatinib with an mTOR inhibitor (NCT00993499) are ongoing [101].

Conclusion

Targeting the EGFR has proven to be a fruitful strategy in combating NSCLC. Gefitinib and erlotinib should be standard first-line therapy in patients with EGFR mutations. Irreversible TKIs will likely provide another step forward, but the questions of how and when we use them need to be answered, with much of the current data having been presented only in abstract form and thus needing to be interpreted with caution. Drugs in this class tend to be well tolerated and they exhibit the typical EGFR toxicities of rash and diarrhea – perhaps more frequently than the reversible EGFR TKIs. Dacomitinib (PF299804) and afatinib (BIBW 2992) appear the most promising and are the only two drugs being tested in Phase III trials in NSCLC currently.

Future perspective

The next 5–10 years are likely to see further evaluation of the irreversible EGFR TKIs. Studies that are already underway should help to define the role of

Executive summary

Background

- Non-small-cell lung (NSCLC) cancer accounts for a large number of cancer related deaths.
- The EGFR is overexpressed in 40–80% of NSCLC and thus is an attractive therapeutic target.

Current evidence for the reversible (first generation) EGFR tyrosine kinase inhibitors

- There is good evidence that the reversible inhibitors gefitinib and erlotinib are effective, particularly in patients with mutations in the gene that encodes the EGFR.
- Most patients inevitably develop resistance to the reversible EGFR inhibitors.

Mechanisms of resistance to EGFR tyrosine kinase inhibitors

- The T790M mutation and MET amplification are the two most common causes for acquired resistance.

Irreversible EGFR inhibitors

- The irreversible inhibitors covalently bind the EGFR potentially making them more potent.
- Of those tested, dacomitinib and afatinib appear the most promising.
- One role for the irreversible inhibitors may be in overcoming resistance to first-line therapy with reversible EGFR inhibitors.
- There are a number of large trials ongoing that will help determine the place for the irreversible EGFR inhibitors in the treatment of NSCLC.

these agents, either as a replacement for the existing first-generation inhibitors of EGFR or as a way to delay and/or overcome the emergence of resistance to them. However, the results of well-designed and conducted studies are needed to identify the place of these agents in the treatment of lung cancer.

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- ▪ of interest
- ▪▪ of considerable interest

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