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EGFR-targeted therapies in lung cancer: predictors of response and toxicity

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Abstract

The EGFR pathway has emerged as a key target in non-small-cell lung cancer. EGF receptor (EGFR) inhibition in non-small-cell lung cancer is achieved via small molecular tyrosine kinase inhibitors, such as erlotinib or gefitinib, or monoclonal antibodies such as cetuximab. A growing body of evidence is identifying potential molecular predictors of response and toxicity. This includes tumor-related molecular markers, such as *EGFR* mutation and copy number, as well as germline markers such as polymorphisms in *EGFR* or EGFR pathway-related genes. This review focuses on the current state of knowledge of predictors of response and toxicity to EGFR inhibitors in lung cancer.

Keywords

cancer genetics; EGFR; lung cancer; predictive markers

The treatment of non-small-cell lung cancer (NSCLC) has been revolutionized by the development of targeted agents. The EGFR pathway has emerged as a key target in NSCLC. A member of the ErbB receptor tyrosine kinase family, which also includes ErbB2 (her2), ErbB3 and ErbB4, the EGF receptor (EGFR) is a transmembrane protein consisting of an extracellular binding domain, a hydrophobic transmembrane segment and a cytoplasmic tyrosine kinase domain. In response to ligand binding, EGFR is activated via dimerization and subsequent autophosphorylation of the tyrosine kinase domain. Phosphorylation activates downstream pathways including the MAPK, PI3K/AKT and STAT signaling pathways and ultimately stimulates cell growth and proliferation [1]. Overexpression of EGFR family members has been seen in a variety of solid tumors, and targeted agents against this family of receptors have been a focus of development [2].

In lung cancer, EGFR is targeted via small molecular tyrosine kinase inhibitors (TKIs), such as erlotinib or gefitinib, or monoclonal antibodies such as cetuximab (Figure 1). A growing body of evidence is identifying molecular predictors of response and toxicity. This includes tumor related molecular markers, such as *EGFR* mutation, copy number and immunohistochemical protein-expression, as well as germline markers such as polymorphisms in *EGFR* or *EGFR*-related genes. This review focuses on the current state of knowledge of predictors of response and toxicity to EGFR inhibitors in lung cancer.

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Clinical background

Small molecular TKIs

Erlotinib and gefitinib are both small molecular TKIs of EGFR. Despite similar promise in early studies, only erlotinib is currently approved in the USA for the treatment of NSCLC. BR. 21, a randomized Phase III trial of erlotinib versus placebo in previously treated patients with advanced NSCLC, showed significant improvement in survival with erlotinib [3]. In this study, 731 patients with one–two prior chemotherapy regimens for advanced NSCLC were randomized in a 2:1 fashion to receive erlotinib or placebo. Response rate was 8.9% in the erlotinib group and less than 1% in the placebo group. Overall survival was significantly improved in the erlotinib group, at 6.7 months versus 4.7 months.

Although gefitinib also had promising response rates in Phase II studies [4,5], an overall survival (OS) benefit was not shown in IRESSA™ Survival Evaluation in Lung Cancer (ISEL), the randomized Phase III trial of gefitinib versus placebo [6]. Some researchers have postulated that differences in dose (erlotinib was dosed at the maximum tolerated dose [MTD], whereas gefitinib was dosed well below its MTD) may account for these different findings. In addition, ISEL and BR.21 had different eligibility requirements regarding progression, with ISEL, but not BR.21, requiring patients to have progressed within 90 days on the prior chemotherapy regimen [7]. Gefitinib in the USA is currently only used in patients who are experiencing ongoing benefits or are on clinical trials, although it is on the market in Japan, Korea and several other Asian countries. However, of note, are several large trials that have investigated gefitinib in comparison to docetaxel in the previously treated NSCLC setting [8–10], and in general have shown comparable efficacy results, with the INTEREST trial, which had 1466 patients, demonstrating noninferiority [9].

Monoclonal antibodies

Cetuximab, a monoclonal antibody to EGFR, may also have a benefit in NSCLC. A recently reported Phase III trial compared cisplatin/vinorelbine with cisplatin/vinorelbine and cetuximab in the treatment of first-line NSCLC [11]. A total of 1125 patients with advanced NSCLC whose tumors expressed EGFR were randomized in a 1:1 fashion to cisplatin/vinorelbine versus cisplatin/vinorelbine with cetuximab. Although no statistically significant difference in progression free survival (PFS) was seen, there was a 1-month improvement in OS favoring the cetuximab arm.

Tumor markers of response

EGFR mutations

Retrospective analyses consistently demonstrated clinical predictors of response to the EGFR TKIs, such as Asian ethnicity, female gender, adenocarcinoma and bronchoalveolar histology, and nonsmoking history [12,13]. In addition to clinical correlates of response to EGFR inhibition, mutations in the *EGFR* gene have been discovered that are associated with response [14,15]. Lynch *et al.* reported in-frame deletions and missense mutations involving the EGFR tyrosine kinase domain in eight out of nine patients responsive to gefitinib who had tumor tissue available. These mutations were not found in the matched normal tissue of the same patients, or in the tumor tissues of seven nonresponding patients [14]. Similarly, Paez *et al.* found mutations in the EGFR tyrosine kinase domain in all of five tumor samples from responding patients and none of four tumor samples from nonresponders [15]. *In vitro* studies showed that in the presence of EGF the mutated EGFR had significantly increased and prolonged activation as compared with wild-type. The mutated receptors were also more sensitive to inhibition by gefitinib [14].

These activating *EGFR* mutations localize to a small region in the *EGFR* gene that encodes the tyrosine kinase domain. The most common, now classical, mutations are an in-frame deletion in exon 19 and a missense mutation at codon 858 that leads to an arginine to leucine substitution (L858R). The presence of these mutations is closely correlated to clinical and pathologic factors, all of which were clinically observed to be associated with response to EGFR TKIs: female gender, Asian ethnicity, adenocarcinoma histology, never-smoking history [16].

Several Phase II studies have attempted to define the response rates and clinical outcomes of a strategy of using EGFR TKIs in patients selected for the presence of *EGFR* mutations (Table 1). Several Japanese studies have demonstrated response rates of 75–90% to gefitinib among patients with *EGFR* mutations, with a median PFS of 7.7–11.5 months [17–20]. A North American study showed response rates of 55% with median PFS of 9.2 months [21]. Of note, this study included atypical *EGFR* mutations in addition to the classical exon 19 deletion and L858R mutations. In a Spanish trial, treatment with erlotinib to patients with *EGFR* mutations yielded a response rate of 82% and median time to progression (TTP) of 13.3 months [22].

Preliminary results were recently reported of The First Line IRESSA Versus Carboplatin/Paclitaxel in Asia study (IPASS), in which 1217 patients who were never/light smokers were randomized to receive gefitinib or carboplatin and taxol. In this Asian population, 453 (74.4%) patients in the gefitinib group experienced disease progression, compared with 497 (81.7%) patients in the chemotherapy arm (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.65–0.85; $p < 0.0001$). When analyzed by *EGFR* mutation status, among *EGFR* mutation-positive patients, PFS was significantly improved among those treated with gefitinib compared with those treated with carboplatin/paclitaxel (HR: 0.48; $p < 0.0001$). For *EGFR* mutation-negative patients, however, the chemotherapy arm did better (HR: 2.85; $p < 0.0001$) [23]. These results are preliminary and OS results are awaited; however they provide an intriguing insight into the potential of targeted treatment based on *EGFR* mutation status.

Although response rates are high among patients with *EGFR* mutations, both *de novo* and acquired resistance remain issues. Numerous studies suggest that the atypical *EGFR* mutations are significantly less predictive of response as compared with the classical mutations. In addition, acquired resistance can develop via several mechanisms. The first described acquired resistance mechanism was a secondary *EGFR* mutation, T790M, which causes a threonine to methionine change at position 790 in the catalytic cleft of the EGFR tyrosine kinase domain. The methionine substitution introduces a bulkier side chain at this position, causing steric hindrance that is thought to interfere with binding of erlotinib [24]. Recently, MET amplification has also been identified as a mechanism of secondary resistance [25,26].

EGFR copy-number

Increased *EGFR* copy-number has also been reported to be associated with response and survival to EGFR TKIs. Capuzzo *et al.* evaluated tumors from 102 NSCLC patients treated with gefitinib for *EGFR* status by fluorescence *in situ* hybridization (FISH), DNA sequencing and immunohistochemistry [27]. Patients with gene amplification (presence of tight *EGFR* gene clusters and a ratio of *EGFR* gene to chromosome of greater than or equal to 2, or greater than or equal to 15 copies of *EGFR* per cell in 10% or more of analyzed cells) or high polysomy (≥ 4 copies in $\geq 40\%$ of cells) had significantly improved response, TTP and OS compared with those with no or low copy-number. Interestingly, gene copy-number does not seem to correlate with the reported clinical predictors of response. In an analysis of patients with adenocarcinoma or bronchioloalveolar carcinoma treated with gefitinib, Hirsh *et al.* reported that increased *EGFR* copy-number detected by FISH was associated with improved survival [28]. In a prospective Phase II trial, patients who were never smokers or were *EGFR* FISH- and phospho-Akt-positive were treated with gefitinib [29]. Overall response was high in this selected

population, at 48%, with median TTP of 6.4 months. *EGFR* FISH-positive patients had significantly better outcomes than FISH-negative patients, with response rates of 68% versus 9.1%, and TTP of 7.6 versus 2.7 months. *EGFR* mutations were also tested in this trial and patients with exon 19 or 21 mutations had significant higher response rates compared with wild-type patients.

EGFR copy-number has also been evaluated in relation to response to the monoclonal antibody cetuximab. Of 221 patients enrolled in a Southwest Oncology Group (SWOG) trial of chemotherapy with cetuximab versus chemotherapy followed by cetuximab in advanced NSCLC, 76 patients were assessable for *EGFR* FISH [30]. 59% of these patients were classified as FISH-positive, based on four or more gene copies per cell in 40% or more of cells, or gene amplification. Response rates were numerically higher in the FISH-positive population, although the difference was not statistically significant. Interestingly, PFS (6 months vs 3 months) and OS (15 months vs 7 months) were significantly better in the FISH-positive patients compared with FISH-negative patients in this retrospective analysis.

Analysis of large randomized controlled trials

Molecular analysis of the large randomized trials of the *EGFR* TKIs has been carried out to assess whether *EGFR* mutation or copy number significantly predicts outcomes. Of the 731 patients in the BR.21 trial, adequate tissue sample was available for 328 [31]. Of these, 325 were analyzed for immunohistochemistry (IHC), 197 for *EGFR* mutations and 221 for *EGFR* copy-number. Response rate was significantly higher among patients with high polysomy or amplification, but was not associated with *EGFR* mutations. However, of note is that 24 of the 45 mutations found were novel mutations rather than the classical exon 19 deletions or L858R that would be expected to have high response rates. Subsequent reanalysis with more sensitive methods for *EGFR* mutation detection in BR.21 showed higher response rates and a trend toward improved survival with erlotinib among those with exon 19 deletion or exon 21 L858R mutations [32]. Analysis of the ISEL trial has also been conducted, and showed high *EGFR* copy-number to be associated with survival; patients with *EGFR* mutations in this trial had higher response rates but there were not sufficient data for survival analysis [33]. Other studies have shown a close association of *EGFR* mutation with response: analysis of the the IRESSA dose evaluation in advanced lung cancer (IDEAL) study showed that 46% of those with *EGFR* mutation had response, compared with 10% of mutation-negative patients [34]. Patients with *EGFR* amplification also had a trend toward higher response to gefitinib, 29% versus 15% [34].

EGFR immunohistochemistry

EGFR expression levels as measured by IHC have not been shown to correlate with response to *EGFR* TKIs [35,36]. In lung cancer, the one positive trial using the monoclonal antibody cetuximab was a trial that selected for patients with *EGFR* expression [11]. However, most studies of cetuximab have not shown an association with *EGFR* IHC and response [37]. In colorectal cancer, a Phase III trial compared cetuximab and irinotecan to cetuximab monotherapy in the irinotecan failure setting. Although immunohistochemical evidence of *EGFR* expression was required for entry into the trial, the degree of *EGFR* expression, either in terms of percentage of *EGFR*-expressing cells or *EGFR* staining intensity, did not correlate with response rate [38]. Therefore, although the FLEX trial, which showed a survival benefit for the addition of cetuximab to chemotherapy in the treatment of advanced disease, selected patients based on *EGFR* expression, it remains to be seen whether *EGFR* expression is truly associated with cetuximab outcomes.

Kras mutation

Kras mutations in lung cancer appear, in general, to be exclusive to *EGFR* mutations and are more associated with smoking [39,40]. *Kras* mutations have been associated with resistance to EGFR TKIs. Pao *et al.* reported that nine out of 38 (24%) tumors refractory to gefitinib or erlotinib had *kras* mutations, while none of 21 sensitive tumors had *kras* mutations [41]. Similarly, van Zandwijk *et al.* found no *kras* mutations among responders to gefitinib in an expanded access program [42]. In a retrospective analysis of TRIBUTE, the randomized Phase III trial of chemotherapy with or without erlotinib in the first-line NSCLC setting, Eberhard *et al.* reported worse TTP and survival among *kras* mutant patients treated with chemotherapy with erlotinib as compared with chemotherapy alone, although it should be noted that numbers are small in this subset analysis [43]. In BR.21, response to erlotinib was lower among *kras* mutant patients than wild-type, with the only *kras* mutant patient who responded also having *EGFR* amplification. There was also a trend toward worse survival among *kras* mutant patients treated with erlotinib, while *kras* wild-type patients treated with erlotinib had improved survival [32].

Interestingly, multiple reports in colorectal cancer have shown a negative correlation of *kras* mutation with response to the EGFR monoclonal antibody cetuximab [44–48]. Analysis of the Phase III CRYSTAL trial, irinotecan with fluorouracil and folinic acid (FOLFIRI) with or without cetuximab in the first-line metastatic colorectal setting, showed that among *kras* wild-type patients, the addition of cetuximab was associated with improved response and PFS. However, among *kras* mutant patients, there was no difference in response or PFS [49]. It remains to be seen whether *kras* mutations can predict responsiveness to cetuximab in lung cancer.

Germline *EGFR* polymorphisms & response & toxicity

Polymorphic variation in *EGFR* & *EGFR*-related genes

Polymorphisms in *EGF* and *EGFR* have been identified that are thought to be functional and influence gene-expression, promoter activity and protein production [50–56]. The CA simple sequence repeat 1 (*CA-SSR1*) is a highly polymorphic locus in intron 1 of *EGFR*, containing 14–21 CA dinucleotide repeats [50,57]. Length of the CA repeat has been inversely correlated with *EGFR* gene transcription, with shorter alleles having higher transcription [51]. In tumors, short CA repeats were associated with elevated EGFR expression compared with those with long CA repeats [52].

Other polymorphisms in *EGFR* have also been reported that are thought to be functional. The $-16G/T$ polymorphism (rs712829) is located in the promoter region of *EGFR* and encodes a change from guanine to thymine. This polymorphism is located in an important binding site for the transcription factor Sp1, and the T allele is associated with increased EGFR expression [53]. The $-91C/A$ polymorphism (rs712830) is also located in the *EGFR* promoter region and the variant form may be associated with differential protein production [58,59]. The *R497K* polymorphism (rs11543848) encodes an A->G alteration resulting in a substitution of arginine by lysine. The Lys allele is associated with decreased activity of EGFR [54].

Ethnic variation has been described in these polymorphisms, which is interesting in light of different responsiveness to EGFR inhibitors by ethnicity. Asian ethnicity is associated with longer CA dinucleotide repeats, while the variant forms of the $-216G/T$ and $-191C/A$ polymorphisms are less common [58,59]. Interestingly, the polymorphic variants associated with increased EGFR production were rare in Asians compared with other ethnicities.

Other polymorphisms in the EGFR pathway that have been investigated include variations in *EGF*, *ABCG2* and cyclin *D1* among others (Table 2). EGFR TKIs appear to be substrates for

multidrug resistance efflux transporter proteins such as ABCG2, which appears to actively pump the drug from cells [60–62]. Functional polymorphisms in *ABCG2* have been described that alter the expression or activity of the protein [63,64], leading to investigations of whether these polymorphisms may affect outcomes in patients treated with EGFR TKIs.

Polymorphisms & clinical outcomes in EGFR TKI treated lung cancer

Several studies have investigated the question of whether polymorphisms in EGFR-related pathways are predictors of response or toxicity to EGFR TKI therapy in lung cancer.

Many of these studies have focused on the intron 1 *CA* repeat polymorphism. Although there are limitations to the studies presented, including relatively small numbers, retrospective nature of the analysis, and nonhomogenous definitions for what is considered a short versus long repeat length, in general the studies seem to suggest that shorter *CA* repeat length is associated with better response and survival in patients treated with EGFR TKIs.

Ichihara *et al.* performed a retrospective analysis of 137 Japanese patients who had received gefitinib [65]. Of these, 98 had specimens available for analysis that included *EGFR* and *kras* mutations, *EGFR* copy-number and *EGFR* polymorphisms, including the intron 1 *CA* repeat, $-216G/T$ and $-191C/A$ polymorphisms. They found that the classical *EGFR* mutations predicted sensitivity to gefitinib. Although none of the polymorphisms studied were significantly associated with response or survival, there was a trend toward shorter *CA* repeats being associated with prolonged survival among those with a classical drug-sensitive *EGFR* mutation. Long *CA* was defined as length of the short allele equal to or greater than 19, or sum of the two alleles equal to or greater than 39 or more; short *CA* defined as length of short allele less than 19 or sum of two alleles less than 39.

Similarly, Han *et al.* retrospectively analyzed 86 Korean patients treated with gefitinib for *EGFR* mutation and *CA* repeat polymorphism [66]. Again, the classical *EGFR* mutations were significantly associated with response and survival. In addition, there was a trend towards higher response rates among patients with low *CA* repeats, defined as sum of two alleles less than or equal to 37 (25 vs 13%; $p = 0.16$). In multivariate analysis, low *CA* repeat was associated with high response and TTP, independent of mutation status.

The association of improved outcomes with shorter *CA* repeats was also reported by Nie *et al.*, who analyzed 70 Chinese patients who had been treated with gefitinib for the *CA* repeat polymorphism and *R497K* SNP [67]. They found that patients with shorter repeats, defined as any allele less than or equal to 16, had better response, with partial response of 58% compared with 28% for those where both alleles were less than 16. In addition, patients who had any allele 16 or less had a median survival of 20 months, compared with 11 months for those where both alleles were greater than 16.

In a study of a predominantly Caucasian population, Liu *et al.* investigated the $-216G/T$, $-191C/A$, intron 1 and Arg497Lys polymorphisms among 92 North American NSCLC patients treated with gefitinib [68]. Shorter *CA* repeats, defined as 16 or fewer repeats, were associated with improved PFS. In addition, the T allele of the $-216G/T$ polymorphism was associated with improved PFS.

However, not all studies have confirmed the association with the intron 1 *CA* polymorphism. Gregorc *et al.* evaluated 175 Caucasian patients treated with gefitinib for *EGFR* intron 1, $-216G/T$ and $-191C/A$ polymorphisms [69]. These authors did not find any association with the intron 1 *CA* repeat polymorphism. However, those with the $-216/-191$ haplotype *G-C* had lower response rates.

In addition to the *EGFR* polymorphisms, much interest has centered on polymorphisms in *ABCG2* as a mediator of drug toxicity. *ABCG2* is a polymorphic efflux transporter protein that has been shown to actively transport *EGFR* TKIs such as gefitinib and erlotinib [70]. Expression of *ABCG2* has been shown to protect *EGFR* signaling dependent cells from death on exposure to gefitinib [60]. Since SNPs have been described that affect the expression and activity of *ABCG2* [63,64,70], it has been hypothesized that these SNPs may affect individual efficacy and toxicity.

The *ABCG2* 421C>A (Q141K) polymorphism results in a glutamine to lysine substitution in codon 141. The variant has been associated with low *ABCG2* expression levels [63,64]. Patients carrying the 421C>A variant have been shown to have significantly higher drug accumulation [70]. Investigators have hypothesized that increased steady state exposure to *EGFR* TKI would increase the risk for drug-induced toxicity. In 124 patients treated with gefitinib, the *ABCG2* 421C>A polymorphism was significantly associated with diarrhea. A total of 44% of patients with the variant developed diarrhea compared with only 12% of those who were homozygous wild-type [71].

Rudin *et al.* reported a prospective trial investigating pharmacogenomic and pharmacokinetic determinants of skin rash and diarrhea among 80 patients with NSCLC, head and neck cancer, and ovarian cancer treated with erlotinib [72]. Polymorphisms in *EGFR*, *CYP3A4* and *3A5*, as well as *ABCG2*, were investigated to assess for association with toxicity. Several novel *ABCG2* polymorphisms that were associated with differential *ABCG2* expression levels were investigated in this study, in addition to previously described SNPs. Skin toxicity seemed to be associated with trough erlotinib concentration and variability in the *EGFR* intron 1 polymorphism, while diarrhea was associated with two linked polymorphisms in *EGFR* promoter, -216G/T and -191C/A. The newly identified *ABCG2* polymorphisms, 1143C/T and -15622C/T, were associated with differential erlotinib concentrations, but there was not a definitive association with toxicity.

In addition to skin rash and diarrhea, interstitial lung disease (ILD) is a well described phenomenon to *EGFR* TKIs. Although studies suggest clinical predictors for ILD such as gender, smoking history and coincidence of interstitial pneumonia [73], there has not yet been data regarding potential molecular predictors of this toxicity.

Polymorphisms & clinical outcomes to *EGFR* antibodies

To date there is little reported on predictors of cetuximab responsiveness in lung cancer. There have been studies in colorectal cancer patients treated with cetuximab that offer some insight into potential avenues of study in lung cancer [74–77]. In general these studies have focused on polymorphisms of *EGF* and *EGFR* such as those described in the sections above. For example, Goncalves *et al.* found that a variant of exon 13 in *EGFR* (R421K) was associated with improved PFS and OS in colorectal cancer patients treated with cetuximab and irinotecan [77]. In addition, interest has focused on polymorphisms of the immunoglobulin-G fragment-C receptor (FcγR). The Fcγ receptors are of interest as cetuximab is thought to mediate antibody-dependent cell-mediated cytotoxicity against cancer cells (ADCC), and the effectiveness of ADCC may depend on the activation of effector cells after engagement with the Fcγ receptors [77–79]. The V/V genotype of the *FCGR3A-V158F* polymorphism has been associated with higher response to rituximab in follicular non-Hodgkin's lymphoma, and the V allele is thought to mediate ADCC more effectively [78]. The H/H genotype of the *FCGR2A-H131R* polymorphism has also been shown to be predictive of response to rituximab [79].

Analyses of the *EGFR* pathway polymorphisms in relation to cetuximab outcomes have yielded conflicting results, with disparate findings reported from several small series [71,74–76]. For example, Graziano *et al.* reported that among 110 colorectal cancer patients treated with

cetuximab and irinotecan, the *EGFR* intron 1 *S/S* and *EGFR* 61*G/G* genotypes were associated with better OS, while there was no association with *EGF*, cyclin D1, and *FcγR* polymorphisms [74]. However, among 39 colorectal patients treated with cetuximab, Zhang *et al.* reported associations with PFS for the *FCGR2A-H131R* and *FCGR3A-V158F* polymorphisms [75,76]. They also reported the A allele of the *EGF* 61*A/G* polymorphism was associated with better survival, which is contrary to the Graziano results.

Predictors of cetuximab toxicity are also being investigated. Graziano *et al.* also investigated the *EGF*, *EGFR*, cyclin D1 and *FcγR* polymorphisms in relation to skin toxicity among patients treated with cetuximab and irinotecan, and found that *EGFR* intron 1 short allele carriers were more prone to have grade 2–3 skin toxicity compared with those who carried the long alleles [74].

These findings in colorectal cancer are clearly preliminary and limited by small numbers but, as increasing numbers of patients with lung cancer are treated with cetuximab, would be potential targets for further study.

Conclusions

Currently, EGFR inhibition is a valid strategy in the treatment of advanced NSCLC. As EGFR inhibitors, such as the TKI erlotinib, and monoclonal antibodies such as cetuximab, emerge as an important part of the treatment strategy for NSCLC, finding better predictors of response, toxicity and survival will be critical to identifying particular populations of patients who might derive the most benefit.

Future perspective

Much work has been carried out to identify molecular predictors of response and survival outcome with treatment with EGFR inhibitors. Tumor-associated somatic mutations and changes in copy number have been most extensively studied in relation to EGFR TKIs. Germline polymorphisms also appear to have a role in management, with *EGFR* polymorphisms such as the intron 1 *CA* repeat polymorphism and polymorphisms in *ABCG2* being shown to affect response and toxicity to EGFR TKIs. Less is known about potential molecular markers of prediction for EGFR antibodies such as cetuximab, but investigations are ongoing.

Executive summary

Clinical background

- Erlotinib, an EGF receptor (EGFR) tyrosine kinase inhibitor (TKI), improves survival in previously treated, advanced non-small-cell lung cancer (NSCLC) patients compared with placebo. Cetuximab, an EGFR antibody, was recently shown to improve survival when added to chemotherapy in the first-line treatment of advanced NSCLC.

Tumor markers of response

- Somatic mutations in *EGFR* have been identified that are associated with response, with the exon 19 deletion and L858R substitution being the classical mutations associated with response to EGFR TKIs.
- EGFR copy-number has also been identified as a predictive marker, with high polysomy or amplification being associated with response and survival in those treated with EGFR TKIs.

Germline polymorphisms & response, & toxicity

- Multiple germline polymorphisms have been studied as predictors of outcome.
- The *EGFR* intron 1 *CA* repeat polymorphism has been most extensively studied, and most reports suggest that shorter repeat lengths, which is associated with higher transcription, are associated with better response. Polymorphisms in *ABCG2* have also been shown to be associated with toxicity.

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Figure 1. Mechanisms of action of anti-EGFR drugs

Inhibition of cancer cell proliferation and invasion, metastasis and tumor-induced neoangiogenesis. Induction of cancer cell cycle arrest and potentiation of antitumor activity of cytotoxic drugs and radiotherapy.

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Table 1
Phase II studies using EGFR tyrosine kinase inhibitors in EGFR mutation-positive patients.

Study	n	Treatment	Response rate median (%) (95%CI)	PFS median (95% CI)	Ref.
Asahina <i>et al.</i>	16	Gefitinib	75 (48–93)	8.9 mo (6.7–11.1)	[17]
Yoshida <i>et al.</i>	21	Gefitinib	91 (70–99)	7.7 mo (6–...)	[18]
Inoue <i>et al.</i>	16	Gefitinib	75 (54–96)	9.7 mo (7.4–9.9)	[19]
Tamura <i>et al.</i>	28	Gefitinib	75 (58–91)	11.5 mo (NR)	[20]
Sequist <i>et al.</i>	34	Gefitinib	55 (33–70)	9.2 mo (6.2–11.8)	[21]
Paz-Ares <i>et al.</i>	37	Erlotinib	82 (66–92)	13.3 mo (NR)	[22]

CI Confidence interval; EGFR; EGF receptor; Mo: Months; NR: Not reported; PFS: Progression free survival; TKI: Tyrosine kinase inhibitor.

Table 2

Selected EGFR and associated pathway polymorphisms.

Polymorphisms	Proposed function
<i>EGFR</i> Intron 1 (CA) _n	Shorter length associated with higher EGFR gene transcription
<i>EGFR</i> -216 G/T	T allele associated with increased promoter activity
<i>EGFR</i> -191 C/A	A allele associated with higher protein production
<i>EGFR</i> R497K A -> G	A -> G alteration resulting in substitution of Arg by Lys Lys associated with decreased activity of EGFR
<i>EGF</i> +61 A/G	A allele associated with less EGF production
<i>ABCG2</i> 421C/A (Q141K)	A allele associated with reduced transport of EGFR TKIs
<i>ABCG2</i> -15994G/A	A allele associated with higher ABCG2 expression
<i>ABCG2</i> -15622C/T	T allele associated with lower ABCG2 expression
<i>ABCG2</i> 16702G/A	A allele associated with higher ABCG2 expression
<i>ABCG2</i> 1143C/T	T allele associated with lower ABCG2 expression
<i>FcGR3A</i> 158V/F	T -> G alteration resulting in Val to Phe at position 158; Val associated with stronger binding to IgG1 and mediates antibody-dependent cell-mediated cytotoxicity activity more effectively
<i>FcGR2A</i> 131H/R	G -> A alteration resulting in His to Arg at position 131; His thought to mediate antibody-dependent cell-mediated cytotoxicity more effectively

EGFR: EGF receptor TKI: Tyrosine kinase inhibitor.