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Is there a role for epidermal growth factor receptor tyrosine kinase inhibitors in epidermal growth factor receptor wild-type non-small cell lung cancer?

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Abstract

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer with a world-wide annual incidence of around 1.3 million. The majority of patients are diagnosed with advanced disease and survival remains poor. However, relevant advances have occurred in recent years through the identification of biomarkers that predict for benefit of therapeutic agents. This is exemplified by the efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for the treatment of EGFR mutant patients. These drugs have also shown efficacy in unselected populations but this point remains controversial. Here we have reviewed the clinical data that demonstrate a small but consistent subgroup of EGFR wild-type patients with NSCLC that obtain a clinical benefit from these drugs. Moreover, we review the biological rationale that may explain this benefit observed in the clinical setting.

Key words: Non-small cell lung cancer; Tyrosine kinase inhibitors; Epidermal growth factor receptors

Core tip: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are well established as the treatment of choice in EGFR-mutant non-small cell lung cancer. However, they are approved and have shown efficacy in patients with wild-type disease. Here, we review the clinical data showing this consistent benefit in a subgroup of patients and the potential biological mechanisms of this clinical effect.

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CLINICAL ACTIVITY OF ERLOTINIB IN STUDIES WITH EGFR WILD-TYPE NSCLC PATIENTS

The activity of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) patients harbouring EGFR mutations has changed the way we diagnose and treat patients. Since the role of oncogenic driver mutations was first recognised, several other genes have been identified as predictors of dramatic and sustained response to other targeted therapies in lung cancer.

Despite this tight link between driver and benefit with specific drugs, we have targeted agents, such as erlotinib or gefitinib, approved for the treatment of molecularly unselected NSCLC patients. Since the design of the trials[1,2] that led to the approval of erlotinib in Western countries or of gefitinib in Asia did not include obligatory assessment of molecular status, some have argued that the benefit observed with TKI *vs* placebo could derive from the undetected EGFR-mutant population in these trials. Other studies have demonstrated activity of EGFR-TKIs in wild-type (wt) EGFR patients with advanced NSCLC (Table 1). This happens in studies treating unselected populations of NSCLC patients, but does it hold true when we select for EGFR-wt tumours? There are three studies[3-5] that have put this into question. The TAILOR trial[3] demonstrates superiority, in terms of progression-free survival (PFS), of docetaxel *vs* erlotinib in second-line treatment in EGFR-wt NSCLC patients. The DELTA trial[4] found that, in a pre-specified subgroup analysis, the EGFR-wt population did better in terms of PFS with docetaxel *vs* erlotinib[4]. The third study[5] compares gefitinib to pemetrexed in an Asian population and demonstrates superiority of pemetrexed in the second-line setting in terms of response rates (RR) and PFS.

Although for the general population of wt patients the benefit of erlotinib might be inferior to chemotherapy, there are still patients who respond and achieve disease control with EGFR-TKIs in those trials. Here, we review the clinical data supporting this potential benefit and the scientific evidence that may underlie the efficacy of EGFR-TKIs in selected EGFR-wt patients.

CLINICAL EVIDENCE FOR ACTIVITY OF EGFR-TKIS IN EGFR-WT NSCLC PATIENTS

Platinum-based doublets are the first-line treatment for unselected advanced NSCLC patients and three drugs are approved for second-line treatment: docetaxel, pemetrexed and erlotinib. Docetaxel has demonstrated effectiveness in prolonging PFS and OS in second-line treatment of NSCLC when compared to single agent chemotherapy[6]. Pemetrexed has shown similar efficacy to docetaxel in the same setting[7].

The BR.21 trial[1] showed that erlotinib improved PFS, OS and quality of life compared with placebo in molecularly unselected patients with advanced NSCLC not suitable for second- and third-line chemotherapy. These results led to the approval of erlotinib in second- and third-line treatment in patients with wt or unknown EGFR mutations. Although EGFR-TKIs are clearly superior to chemotherapy in patients with EGFR- mutant NSCLC[8,9], their role in wt patients is still controversial. Several trials have compared EGFR-TKIs with chemotherapy in unselected patients with NSCLC, but the majority were not properly designed to investigate the treatment benefit according to EGFR mutations, and retrospective analysis according to EGFR genotype was restricted by the high percentage of patients with unknown EGFR status[10].

First-line trials

Combination with chemotherapy: The combination of EGFR-TKIs with platinum-based chemotherapy doublets in the first-line setting was evaluated in phase III trials (Table 1); both gefitinib and erlotinib were studied in combination with cisplatin and gemcitabine (INTACT 1 and TALENT)[11,12] and with carboplatin and paclitaxel (INTACT 2 and TRIBUTE)[13,14]. The addition of gefitinib or erlotinib to standard first-line chemotherapy did not result in a survival benefit in the general population, but in the TRIBUTE study[14], never-smoker patients treated with erlotinib and chemotherapy experienced an improvement in survival. The proportion of patients with a non-adenocarcinoma histology and thus likely to be EGFR-wt ranged from 39.3%-61.6%. No difference in efficacy according to histology was found in the subgroup analysis of these studies. Clinical trial results are summarised in Table 1. It seems that the combination of EGFR-TKIs with chemotherapy in EGFR-wt patients does not provide additional benefit.

Monotherapy: Certain clinical characteristics (adenocarcinoma histology, Asian race, female gender and never-smoking status) were related with an increased probability of response to EGFR-TKIs. The IPASS trial[8] included only patients with these characteristics, comparing the efficacy of first-line gefitinib monotherapy to the combination of carboplatin and paclitaxel. This trial demonstrated the inefficacy of clinical selection in predicting mutational status, as up to 40% of these clinically selected patients were EGFR-wt. Gefitinib was non-inferior to chemotherapy in the general population. The subgroup analysis clearly showed superiority of gefitinib over chemotherapy in patients harbouring EGFR mutations, but also showed that gefitinib was inferior to chemotherapy in EGFR-wt cases. Of note, however, was that the disease control rate with gefitinib in the EGFR-wt population was 39.6%, with one patient achieving a partial response. The results of these trials are summarised in Table 1. Taken together, these trials show a subset of EGFR-wt patients with some benefit from EGFR-TKIs, in general in the form of stabilisation

Table 1 First-line and maintenance phase III trials

Trial	Comparison	Population characteristics	Efficacy in all patients	Efficacy in subgroup enriched for EGFR wt	Mutational analysis	Efficacy by mutational status
INTACT 1[11]	C + Gem + G (n = 730) *vs* C + Gem + P (n = 363)	First line; nonADC, 53.9%; non-Asian, 94.7%	PFS for C + Gem + G, 5.5 mo; PFS for C + Gem + P, 6 mo; P = 0.763; OS for C + Gem + G, 9.9 mo; OS for C + Gem + P, 10.9 mo; P = 0.45	NR	NR	NR
INTACT 2[13]	Cb + T + G (n = 692) *vs* Cb + T + P (n = 345)	First line; nonADC, 44.9%; non-Asian, 95.8%	PFS for Cb + T + G, 5.3 mo; PFS for Cb + T + P, 5 mo; P = 0.056; OS for Cb + T + G, 9.8 mo; OS for Cb + T + P, 9.9 mo; P = 0.638	NR	NR	NR
TALENT[12]	C + Gem + E (n = 580) *vs* C + Gem + P (n = 579)	First line; nonADC, 61.6%; non-Asian 93.6%	PFS for C + Gem + E, 5.9 mo; PFS for C + Gem + P, 6.1 mo; HR = 0.98; P = 0.74; OS for C + Gem + E, 10.7 mo; OS for C + Gem + P, 11 mo; HR = 1.06; P = 0.486	NR	NR	NR
TRIBUTE[14]	Cb + T + E (n = 539) *vs* Cb + T + P (n = 540)	First line; nonADC 39.3%; non-Asian, 96.9%	PFS for Cb + T + E, 5.1 mo; PFS for Cb + T + P, 4.9	NR	n = 228 (21.1%); activating mutation, 29	NR
IPASS[8]	G (n = 609) *vs* Cb + T (n = 608)	First line; only Asians with ADC and never or light former smokers	PFS for G, 5.7 mo; PFS for Cb + T, 5.8 mo; HR = 0.74; P < 0.001		n = 437 (35.9%); activating mutation, 261	EGFR mutated: PFS HR, 0.83; EGFR wt: PFS HR, 2.85; interaction P < 0.001
First-SIGNAL[15]	G (n = 159) *vs* C + Gem (n = 154)	First line; only Asians with ADC and never smokers	PFS for G, 5.8 mo; PFS for C + Gem, 6.4 mo; HR = 1.198, P = 0.138; OS for G, 22.3 mo; OS for C + Gem, 22.9 mo; HR = 0.932; P = 0.604		n = 96 (31%); activating mutation, 42	EGFR mutated: PFS HR, 0.54; EGFR wt: PFS HR, 1.41
SATURN[16]	E (n = 438) *vs* P (n = 451)	Maintenance; no progression after prior platinum-doublet; nonADC, 55%; non-Asian, 85%	PFS for E, 3 mo; PFS for P, 2.77 mo; HR = 0.71; P < 0.001; OS for E, 12 mo; OS for P, 11 mo; HR = 0.81; P = 0.0088	Squamous PFS HR, 0.76; non-Asian PFS HR, 0.75; squamous OS HR, 0.86; non-Asian OS HR, 0.86+	n = 446 (50.1%); EGFR activating mutation, 49	EGFR mutated: PFS HR, 0.10; EGFR wt: PFS HR, 0.78; interaction P < 0.001; EGFR mutated: OS HR, NR; EGFR wt: OS HR, 0.77

ADC: Adenocarcinoma; C: Cisplatin; Cb: Carboplatin; D: Docetaxel; E: Erlotinib; EGFR: Epidermal growth factor receptor; G: Gefitinib; Gem: Gemcitabine; HR: Hazard ratio; NR: Not reported; OS: Median overall survival; P: Placebo; Pem: Pemetrexed; PFS: Median progression free survival; T: Paclitaxel; wt: Wild type.

of disease.

Maintenance therapy trials

The sequential Tarceva in unresectable NSCLC (SATURN) trial[15] was a phase III study that randomised patients without progression after 4 cycles of platinum-doublet chemotherapy to erlotinib or placebo as maintenance treatment. Maintenance therapy with erlotinib produced a modest benefit in terms of PFS (HR = 0.71; P < 0.01) and OS (HR = 0.77; P < 0.008) in the overall population. The subgroup analysis revealed that the benefit was greater in EGFR-mutant patients. However,

this benefit still persisted in EGFR-wt cases, both for PFS (HR = 0.78; *P* = 0.018) and OS (HR = 0.77; *P* = 0.243). One of the main caveats of this study is that maintenance treatment with pemetrexed is currently indicated in non-squamous tumours[16], so the benefit observed in wt patients could be inferior to that offered by pemetrexed. Another phase III study[17] (ATLAS) evaluated the addition of erlotinib to maintenance treatment with bevacizumab after first-line chemotherapy in unselected patients. The addition of erlotinib to bevacizumab improved PFS (HR = 0.71; *P* < 0.001) but not OS (HR = 0.92; *P* = 0.534). It should be noted that the study was not powered to detect differences in OS, it was unblinded after the interim analysis, and further survival follow-up was not pursued based on the low likelihood of observing significant differences between arms. Lastly, a phase III trial[18] evaluating maintenance therapy with gefitinib showed similar results, with an improvement in PFS (HR 0.61; *P* = 0.001) but not in OS (HR = 0.83; *P* = 0.2). Results of the above trials are summarised in Table 1.

Second- and third-line trials

The BR.21[1] and ISEL[19] trials compared erlotinib and gefitinib respectively with placebo and best supportive care in second- and third-line settings in unselected populations.

Despite an RR of only 8%, in the BR.21 trial, erlotinib showed an improvement in OS (6.7 mo with erlotinib *vs* 4.7 mo with placebo; HR = 0.70; *P* < 0.001). This benefit was also observed in patients with squamous histology, a subgroup more likely to be EGFR-wt. In retrospective analysis the results for EGFR-wt patients were similar to the overall population, with an RR of 7% in EGFR-wt patients treated with erlotinib[20,21]. In a retrospective analysis 21 of the 15% of cases with available tissue from the ISEL study, the RR to gefitinib in EGFR-wt patients was 2.6%.

In the INTEREST trial[22], a non-inferiority trial comparing second-line treatment with gefitinib and docetaxel in an unselected population, gefitinib was non-inferior to docetaxel. This non-inferiority was maintained in the non-adenocarcinoma and non-Asian subgroups. The EGFR-mutated cases had better PFS than those with EGFR-wt tumours, but no differences were shown in terms of OS. The RR of EGFR-wt patients treated with gefitinib was 6.6%[23].

The TITAN study[24] included patients who progressed on first-line platinum-doublet chemotherapy in the run-in period shared with the SATURN trial. Second-line erlotinib was compared with docetaxel or pemetrexed. Erlotinib showed a similar efficacy to docetaxel or pemetrexed, but the trial was not powered to detect non-inferiority because it was prematurely halted due to poor accrual. EGFR mutational status was determined in 40% of patients. No differences between treatment arms were shown in the EGFR-wt population. The HORG trial[25] showed no differences in efficacy between erlotinib and pemetrexed in second- or third-line settings in unselected patients. The limited efficacy of pemetrexed in squamous histology may have decreased the performance of the pemetrexed arm. Focusing on EGFR-wt patients, the RR with erlotinib was 7.3%, with a disease control rate of 21.8%.

Recently the TAILOR phase III study[3] compared second-line treatment with erlotinib or docetaxel in EGFR-wt tumours. Docetaxel was superior to erlotinib in terms of PFS (2.9 mo with docetaxel *vs* 2.4 mo with erlotinib; HR = 0.71; *P* = 0.02), and showed a trend towards superiority over erlotinib in OS (OS 8.2 mo with docetaxel *vs* 5.4 mo with erlotinib; HR = 0.73; *P* = 0.05). Despite this, 3% of patients in the erlotinib arm achieved a partial response, and 23% disease stabilisation. In the CTONG 0806 study[26] conducted in China, comparing pemetrexed with gefitinib in EGFR-wt patients, overall results favoured pemetrexed, with PFS of 5.6 *vs* 1.7 mo. However, some benefit was still observed in the gefitinib arm in the form of ORR and disease stabilisation of 2.4% and 12.2%, respectively. The results of second- and third-line phase III trials are summarised in Table 2.

In conclusion, the efficacy of second- and third-line treatment in non-mutant patients with advanced NSCLC is limited. Moreover, the toxicity of chemotherapy, in particular docetaxel, can deteriorate the quality of life of patients at this stage. The main advantages of EGFR-TKIs in this setting are basically the convenience of oral administration and mild and manageable toxicity. Although the studies presented above show limited efficacy of erlotinib or gefitinib for EGFR-wt patients, a response rate of approximately 8% has consistently been observed, with stabilisation in 25% of patients. This small, but significant population may have relative dependence on the EGFR pathway independent of mutational status that may explain these clinical observations.

In the next part of the article, we review potential biological explanations for this clinical effect.

BIOLOGICAL EVIDENCE OFR EGFR INHIBITION IN EGFR WILD-TYPE NSCLC

EGFR pathway

The EGF receptor (EGFR/HER1) belongs to a family of receptors with a common architecture (HER2, 3 and 4). These receptors have an extracellular ligand-binding portion, a single transmembrane helix and an intracellular tyrosine kinase domain and C-terminal tail that serve as a scaffold for adapter molecules. A variety of EGF receptor ligands, mainly amphiregulin, TGF-alpha and EGF for EGFR, upon binding, drive the formation of homo- or heterodimers that activate the receptors and amplify their signal. In cancer cells, the phosphorylation of the tyrosine kinase domain eventually results in the recruitment of intracellular substrates and binding of adaptor molecules that

Table 2 Relevant second- and third-line phase III trials

Trial	Comparison	Population characteristics	Efficacy in all patients	Efficacy in subgroup enriched for EGFR wt	Mutational analysis	Efficacy by mutational status
BR.21[1,21]	E (n = 488) *vs* P (n = 243)	Second line (51%) or third line (49%); nonADC, 50%; non-Asian, 87%	OS for E, 6.7 mo; OS for *P*, 4.7 mo; HR 0.70; P < 0.001	NonADC HR, 0.8; non-Asian HR, 0.8	n = 204 (27.9%); EGFR activating mutation, 34	EGFR mutated: OS HR, 0.55; EGFR wt OS HR, 0.74; interaction P = 0.47
ISEL[20,23]	G (n = 959) *vs P* (n = 480)	Second line (49%) or third line (51%); nonADC 52%; non-Asian, 90%	OS for G, 5.6 mo; OS for *P*, 5.1 mo; HR, 0.89; P = 0.089	NonADC HR < 1.0[1]; non-Asian HR = 0.92	n = 215 (14.9%); activating EGFR mutation, 26	NR
INTEREST[24,25]	G (n = 723) *vs* D (n = 710)	Second line (84%) or third line (16%); nonADC, 44%; non-Asian, 78%	OS for G, 7.6 mo; OS for D, 8 mo; HR, 1.02 (met non inferiority criteria)	NonADC HR < 1[1]; non-Asian HR = 1[1]	n = 297 (20.7%); activating EGFR mutation, 44	EGFR mutated: OS HR, 0.83; EGFR wt: OS HR, 1.02; interaction P = 0.59
TITAN[26]	E (n = 203) *vs* D/Pem (n = 221)	Second line; non-Asian, 86%; nonADC, 55%	OS for E, 5.3 mo; OS for D/Pem, 5.5 mo; HR = 0.96; P = 0.73	Squamous OS HR = 0.86; non-Asian OS HR = 0.94	n = 167 (39.3%); activating EGFR mutation, 18	EGFR mutated: OS HR = 1.19; EGFR wt: OS HR = 0.85
HORG[27]	E (n = 166) *vs* Pem (n = 166)	Second line (57%) or third line (43%); nonADC, 77.5%; non-Asian, 100%	PFS for E, 3.6 mo; PFS for Pem 2.9 mo; P = 0.136; OS for E, 8.2 mo; OS for Pem, 10.1 mo; P = 0.986	Squamous OS HR = 1.97	n = 123 (37%); activating EGFR mutations, 11	NR

[1]HR estimated from forest plot in publication. ADC: Adenocarcinoma; C: Cisplatin; Cb: Carboplatin; D: Docetaxel; E: Erlotinib; EGFR: Epidermal growth factor receptor; G: Gefitinib; Gem: Gemcitabine; HR: Hazard ratio; NR: Not reported; OS: Median overall survival; P: Placebo; Pem: Pemetrexed; PFS: Median progression free survival; T: Paclitaxel; wt: Wild type.

activate downstream signalling pathways. One of the major signalling pathways downstream of EGFR is the Ras-Raf-MAP kinase pathway. Another important target of EGFR signalling is the PI3K-Akt pathway. Lastly, EGFR activation also recruits PKC and Jak/Stat. The activation of these pathways induces transcriptional programmes that result in increased proliferation, survival, motility, and invasion[27].

Different mechanisms for activation of the EGFR pathway have been postulated.

Overexpression of EGFR ligands

Eleven ligands have been reported to bind to the ErbB receptor family, including epidermal growth factor (EGF), transforming growth factor alpha (TGFα), amphiregulin, betacellulin, heparin-binding EGF and epiregulin. These are synthesised as membrane-anchored precursor forms that are then cleaved to generate soluble ligands. In some cases, these membrane-anchored isoforms can also act as biologically active ligands. Moreover, stromal cells have been described as releasing amphiregulin and TGFα. Thus, activation of EGFR by its ligands can happen through paracrine, autocrine and juxtacrine mechanisms[28]. Upon binding, they induce a conformational change in the receptor and activate several signalling pathways (see above).

Preclinical studies have been performed to evaluate the role of these ligands in the response to the treatment with EGFR-TKIs, showing conflicting results. A study by Yonesaka *et al*[29] demonstrated that high levels of amphiregulin (Areg) produced by EGFR-wt NSCLC cells through an autocrine mechanism predicted sensitivity to gefitinib in the form of cell cycle arrest. This happened preferentially by inhibition of signal-regulated kinase 1/2, but not the Akt pathway. In contrast, some studies[30,31] showed that autocrine Areg confers resistance to gefitinib in NSCLC cells through inhibition of apoptosis. In this case, inhibition of Areg secretion by siRNA was able to restore sensitivity to gefitinib in EGFR-wt cell-line models (H358) *in vitro* and *in vivo*. Moreover, addition of recombinant Areg to previously sensitive NSCLC cell lines (H322) conferred resistance to these cells[30]. Intriguingly, Areg reduced acetylation of ku70, preventing the release of the proapoptotic form of BAX and, consequently, inhibiting the gefitinib toxicity in NSCLC cells[31], suggesting a role for the combination of EGFR-TKIs with HDAC inhibitors (see below-EMT). These discrepancies in preclinical data may be due to differential downstream effects produced by the ligands in each particular cell-line model.

Regarding clinical data on EGFR ligands and response to EGFR inhibitors, most studies have focused on the role of amphiregulin and TGFα. A retrospective study by Chang *et al*[32] evaluates amphiregulin expression by immunohistochemistry in NSCLC specimens. This work showed an association between amphiregulin expression (H-score >100) and better OS in patients treated with erlotinib or gefitinib.

Several publications[33,34] have reported on the role of serum levels of circulating amphiregulin (cAreg) and TGFα (cTGFα) in NSCLC patients treated with EGFR-TKIs.

Detection of these circulating markers may allow measurement of the total expression of these markers in different compartments and be a surrogate marker of the EGFR signalling intensity. A Japanese study showed that high levels of cAreg in serum were associated with lack of benefit from gefitinib[33]. In contrast, a study performed in the Netherlands concluded that patients presenting high levels of cAreg benefited from treatment with EGFR-TKIs[34]. The authors speculate that these differences may be based on ethnic differences.

More consistent data have been reported for cTGFα. It seems that high baseline TGFα predicts lack of benefit from erlotinib or gefitinib[33,35] or, accordingly, low levels before treatment predict benefit from EGFR-TKIs[34].

The convenience of measuring circulating levels of a protein to select patients for a treatment underlines the importance of validating these results in prospective trials. Validated cut-offs and techniques for these measurements are essential to ensure the applicability of these findings to day-to-day clinical practice.

Other members of the ERBB family

Upon ligand stimulation, EGFR forms homodimers or heterodimers with the other HER family members. Several studies[36,37] demonstrated the importance of the status of other EGFR family members in response to EGFR-TKIs. HER2 is overexpressed in various cancers through gene amplification that constitutively activates the protein. In lung cancer, HER2 amplification has been identified in a low percentage of patients and has been associated with poor prognosis[36]. HER2 mutations have also been identified in NSCLC in about 2% of patients[37]. The impact of these genetic abnormalities or overexpression of HER2 in the response to EGFR-TKI treatment in NSCLC has been evaluated.

For instance, HER2 mutations seem to predict for resistance to EGFR-TKIs[38] in NSCLC cells, while these remain sensitive to anti-HER2 treatments. In this study, knockdown of mutant HER2 induced cell death and sensitised these cells to EGFR-TKIs. In contrast, amplification/overexpression of the *HER2* gene has been associated with moderate sensitivity to gefitinib and erlotinib[39]. Cell-line studies in NSCLC models show that overexpression of HER2 in EGFR-wt cells enhances sensitivity to gefitinib that acts specifically through the inhibition of the PI3K/Akt pathway[40,41]. In these models, a relevant role of HER3 in the observed response could not be ruled out; either through specific abrogation by gefitinib of HER2/3 heterodimers[40] or by the presence of coexpression of this receptor[41].

In the clinical setting, there is retrospective evidence showing that patients with EGFR-positive tumours (by immunohistochemistry) which harbour high HER2 copy numbers have better response and disease control rates when treated with gefitinib[42]. The clinical data on patients, whose tumours harbour HER2 mutation support the use of drugs such as trastuzumab or afatinib for these patients[37].

As discussed above, HER3 expression has also been associated with sensitivity to EGFR-TKIs. ErbB3 is unique among the ErbB family members because it lacks significant tyrosine kinase activity. However, it heterodimerizes with other members of the family and couples to the PI3K/Akt pathway, initiating intracellular signalling pathways. In preclinical models, it has been shown that EGFR-wt NSCLC cell lines are growth-inhibited by gefitinib when downregulation of the PI3K/Akt pathway is observed through ErbB3[41], and this has also been suggested in pancreatic cancer cells[43].

Results from a clinical study[44] suggest that HER3 expression is a predictor of response to EGFR-TKIs independent of EGFR mutational status, although more data are needed. HER4 mutations have also been identified in lung cancer[45]. The role of this receptor in lung cancer seems to be associated with chemoresistance[46] and there is one study that shows that a HER4 mutant cell line was resistant to gefitinib[39].

Overall, it seems that HER-family receptor status has an impact on the response of wild-type EGFR lung cancer to EGFR-TKIs and that combining EGFR-TKIs with other receptor inhibitors or the use of pan-HER inhibitors could be a promising strategy for the treatment of patients with activation of the HER family members.

Epithelial to mesenchymal transition

Epithelial-to-mesenchymal transition (EMT) is a cellular process that occurs both during critical phases of embryonic development and in carcinogenesis[47]. This transition is characterised by the loss of epithelial markers and acquisition of a mesenchymal phenotype, which enables cancer cells to invade surrounding tissues and generate distant metastases[48]. Loss of E-cadherin expression, a key protein in adhesive junctions between epithelial cells, is central to EMT. Therefore, E-cadherin-negative cells show a more invasive phenotype[47,48]. This process is initiated by the transcriptional factor Snail1. Although Snail1 is induced at the early phases of EMT its expression is not maintained in most mesenchymal cells; instead, E-cadherin silencing is dependent on other transcriptional repressors induced by Snail1, such as Zeb1 and 2[49]. Other markers of a mesenchymal phenotype are expression of vimentin, fibronectin or N-cadherin[47].

EMT has been associated with poor prognosis and chemoresistance in different tumour models[50-52].

Many studies[53-55] have demonstrated a correlation between sensitivity to EGFR-TKIs and EMT in lung cancer. A gene expression analysis[53] in NSCLC cell lines showed a correlation between expression of epithelial- or mesenchymal-related genes and growth inhibitory effect of erlotinib. Cell lines with an epithelial phenotype showed a lower IC_{50} compared to cells with a mesenchymal phenotype[54]. A similar study[55] reported differences in expression of vimentin and fibronectin between erlotinib-sensitive and erlotinib-insensitive cell lines. Cell lines overexpressing fibronectin and/or vimentin were insensitive to growth inhibition by erlotinib *in vitro* and *in vivo*, and no or little expression of these proteins was found in erlotinib-sensitive cells. Conversely, expression of E-cadherin and ErbB3 was found in erlotinib-sensitive cell lines and was absent in insensitive cell lines[20]. Comparable results have been observed using gefitinib in NSCLC, head and neck Squamous Cell Carcinoma (HNSCC) and hepatoma cell lines[56,57], which supports the hypothesis that EMT status is predictive of EGFR-TKI sensitivity. Moreover, Frederick *et al*[56] found gefitinib sensitivity to be more strongly related with epithelial or mesenchymal phenotype than with tumour origin, and, in the gene expression analysis, gefitinib-sensitive NSCLC clustered together with sensitive HNSCC cells, as did gefitinib-resistant cell lines of both histological origins. However, within the two sensitivity groups, HNSCC cells formed a cluster of distinct NSCLC cells.

To explore the clinical relevance of these observations, Yauch *et al*[53] evaluated E-cadherin membranous and cytoplasmatic staining in tumour samples from a subset of patients who had participated in the TRIBUTE trial. E-cadherin staining intensity was determined on a scale of 0-3, and patients divided into two groups: E-cadherin positive (2-3+); and E-cadherin negative (0-1+). No statistically significant differences were found between groups in terms of RR and OS. However, within the E-cadherin-positive staining subgroup, there was a statistical significant difference in time to progression favouring those receiving CHT + erlotinib *vs* those receiving CHT alone (34 *vs* 19.3 wk respectively; $P = 0.003$). Comparable results were observed analysing tumour samples of a subset of patients with chemorefractory NSCLC who had participated in the BATTLE trial[58]. Of 20 KRAS-wt/EGFR-wt tumours that received erlotinib, 8-wk disease control was superior in those tumours with an epithelial phenotype, although this was of borderline significance.

Several pathways have been explored as a mechanistic link between EMT and the EGFR pathway. In cell-line cultures, the biological activity of the EGFR pathway has been related to erlotinib sensitivity. In EGF-stimulated cells, erlotinib inhibited phosphorylation of Akt and Erk independent of EMT status. However, under baseline conditions, this effect could only be observed in epithelial-like cells[53].

The findings presented above point to a common capacity for mesenchymal-like cancer cells for by-passing the EGFR pathway and/or having alternative mechanisms to resist apoptosis and maintain their proliferative potential. Increased Akt and STAT3 activation through elevated expression of Integrin-linked kinase (ILK) was found in gefitinib-resistant hepatoma cell lines with a mesenchymal-like phenotype[57]. ILK is a serine/threonine protein kinase that is localised to focal adhesions and stimulated by engagement of integrins to the extracellular matrix[59]. ILK regulates E-cadherin levels through interaction with transcription factors such as Zeb1 and Snail[60], and up-regulation of ILK has been detected in mesenchymal-like cell lines. Fuchs *et al*[57] found that inhibition of ILK in two EGFR-TKI resistant hepatoma cell lines and mouse xenografts caused a decrease in p-Akt levels and restored cell sensitivity to gefitinib, partly through an EMT. Furthermore, ILK expression has been related to shorter survival and risk of recurrence in Japanese patients with Stage Ia-IIIa resected NSCLC[61].

Acquisition of platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) is another way for mesenchymal-like NSCLC cells to maintain survival independent of EGFR activity. In a study[57] with NSCLC cell lines, both epithelial and mesenchymal-like cells showed expression of PDGF ligands. However, expression of PDGFR alpha and beta was only detected in mesenchymal-like cells. In this study, EGFR blockade by erlotinib showed increased PDGFR autophosphorylation and downstream activation in mesenchymal-like cells. Similar findings were detected in regard to FGFR and FGF-ligand expression and activity. Interestingly, in a cell line that underwent an epithelial-to-mesenchymal-like transition induced by TGF-beta stimulation, increased levels of PDGFR, PDGF-ligands, FGFR, FGF-ligands and transcription factors (Snail, Zeb1 and Zeb2) were detected, along with a significant decrease in erlotinib-sensitivity. Treatment of this cell line with a TGF-beta receptor inhibitor reversed this process and re-sensitised the cells to erlotinib.

Moreover, transfection of E-cadherin in NSCLC cell lines resistant to gefitinib resulted in a decrease in cellular growth that was further enhanced in the presence of gefitinib. The apoptotic effect of gefitinib was increased in transfected cell lines compared to the parental cell controls. The activity of transcription factors such as Snail, Zeb1 and Sip1 ultimately leads to recruiting of histone deacetylases (HDAC) and, consequently, to chromatin condensation and gene silencing. HDAC inhibitors are currently being studied as anticancer treatment[62]. Inhibiting HDAC induces E-cadherin expression[63].

Witta *et al*[64] demonstrated a synergic effect of HDAC inhibitor MS-275 (entinostat) and gefitinib in 4 NSCLC cell lines resistant to EGFR-TKIs. Growth inhibitory and apoptotic effects of gefitinib increased after pre-treatment with 24 h of MS-275, and was similar to the effect of gefitinib alone in a cell line harbouring the L858R mutation. A phase Ⅱ randomised study[64] in non-selected, previously treated patients

with advanced NSCLC failed to show a benefit in PFS with the combination of erlotinib-entinostat *vs* erlotinib-placebo. However, subset analysis showed increased OS in patients with high E-cadherin levels in their tumour samples (9.5 mo *vs* 5.4 mo; $P = 0.03$)[64]. Thus, it appears that patients with a more epithelial-like tumour were the ones who benefited from the combination, while patients whose tumours had mainly lost E-cadherin expression did not. Therefore, reversion of EMT through HDAC inhibition would only be possible in an initial state of transformation, being more effective in preventing EGFR resistance than in restoring it.

Gene signatures

As the status of the EGFR or other family members does not completely explain the potential benefit from EGFR-TKIs, efforts have been made to evaluate gene signatures that may better predict for response to these drugs.

Several studies[65,66] have identified gene expression profiles that discriminate patients who benefit from EGFR-TKIs from those who do not. Kakiuchi *et al*[65] described a 12-gene signature obtained from human lung carcinoma samples with differential expression between responders and non-responders to gefitinib. Interestingly, some of these genes, such as *Areg*, *TGFα* and *ADAM9*, are directly related to the EGFR pathway. They also obtained serum samples from an independent cohort of patients and concluded that those with higher levels of circulating TGFα were classified as non-responders. They finally validated the Areg results with *in vitro* models, suggesting that Areg expression was associated with lack of response to gefitinib. Tan *et al*[66] described that the gene signature is not a strong predictor of benefit from erlotinib.

Another strategy has been to obtain the gene expression signature from lung cancer cell lines and then validate it in independent cell line or tumour samples. In this regard, Balko *et al*[67] and Coldren *et al*[68] generated > 100-gene signatures that exhibited enrichment in signal transduction functions between EGFR-inhibition sensitive and EGFR-inhibition resistant and were more robust than prediction based on mutational status alone.

The clear advantage of this approach is that study of the complexity of the tumour can be addressed by simultaneously evaluating multiple genes that may be involved in the behaviour of a particular tumour. However, in the attempt to limit the number of genes to be used in a platform, we are probably leaving out genes that are more relevant than the ones we include. Further validation in human samples from patients treated with these drugs is warranted.

MicroRNAs

MicroRNAs are regulatory RNAs that are responsible for post-transcriptional gene silencing by degrading the mRNA or preventing its translation. One study[69] using NSCLC-cell-line expression data identified a 13-gene miRNA signature that predicted sensitivity to erlotinib. These miRNAs were involved in the control of the expression of proteins involved in EMT.

There are also studies that identify single miRNAs as predictors of response to EGFR-TKIs. Chen *et al*[70] identify miR-146a as overexpressed in cell-line models with activated EGFR. This microRNA was also a predictor of inhibitory response to erlotinib, gefitinib and afatinib. An additional study[71], based on head and neck cancer cell lines, identifies miR-7 as a tumour-suppressor gene that regulated EGFR expression and downstream signalling and enhanced sensitivity to erlotinib. An unpublished study by Li *et al*[72], performed in NSCLC cell lines and then validated in patients' samples, demonstrates an association between expression of miR-200c, epithelial phenotype and response to EGFR-TKIs in EGFR-wt patients.

This area is currently being actively investigated and will probably provide interesting data on other regulatory mechanisms of EGFR that may affect the response to EGFR-TKIs.

Proteomics

Lastly, there are some publications reporting evidence of serum- or plasma-based assays as predictors of response to EGFR-TKIs. VeriStrat® is the test with the most solid data that we will review here.

VeriStrat® is a commercially available serum- or plasma-based test which uses matrix- assisted laser desorption ionisation (MALDI) mass spectrometry methods. It was developed through a training set of serum samples obtained before treatment from patients who experienced long-term stable disease or early progression on gefitinib therapy[73]. Mass spectra (MS) from these patients' serum samples were used to define eight MS features, differentiating these two outcome groups.

The commercial test uses a fixed set of parameters established during the development phase and assigns each spectrum a binary classification of Good or Poor. Two independent cohorts of patients[73] who were treated with gefitinib or erlotinib confirmed that patients classified as Good had better outcomes than patients classified as Poor (HR for death 0.47, $P = 0.009$ and HR for death 0.33, $P = 0.0007$). VeriStrat® was not predictive of benefit in patients receiving other treatments[73]. A more recent study[74] further validated the role of VeriStrat® as a predictor of benefit from EGFR-TKIs. Good VeriStrat® classification was associated with better outcome in patients in the placebo arm. Regarding prediction of response, Good patients had a higher response rate than poor patients (11.5% *vs* 1.1%, $P = 0.002$), with a Good classification remaining independently correlated with response after adjustment for potential confounding factors. However, for both OS and PFS, VeriStrat® was prognostic but not predictive of differential benefit from erlotinib, leading to doubts about the clinical utility of this test for decision making. A prospective study[75] to test this hypothesis

was finally set up and preliminary data show that patients classified as VeriStrat Poor performed worse when treated with erlotinib compared to chemotherapy.

CONCLUSION

Similar data have been consistently reported about the limited but significant benefit of EGFR-TKIs in a subset of patients with EGFR-wt NSCLC. Many potential biological mechanisms could underlie these observations. However, lack of prospective and validated data preclude drawing robust conclusions. Moreover, combination therapies blocking the EGFR pathway with other "escape" pathways provide an additional potentially beneficial approach to the treatment of patients with somewhat EGFR-dependent tumours. Additional studies specifically designed for the validation of these hypotheses are warranted in order to be able to translate these findings to the clinic.

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