Systemic treatment in EGFR-ALK NSCLC patients: second line therapy and beyond

Over a short period of time, translational research has described a new clinically relevant molecular subset of non-small-cell lung cancer (NSCLC) that is defined by EGFR mutations or EML4-ALK fusions. Today, patients with metastatic disease can achieve survival rates at least double that of patients with wild-type tumors. Through the rational dissection of the mechanisms of drug sensitivity and resistance, promising strategies have been defined to further improve the outcomes of patients with NSCLC. This review adds to a growing body of knowledge into mechanisms of resistance that can be interrogated in NSCLC patients with EGFR mutations or EML4-ALK fusions, as well as strategies to overcome resistance to TKIs.

**KEYWORDS:** EGFR • EML4–ALK • lung cancer • TKI resistance • tyrosine kinase inhibitors

In recent years, diagnosis and treatment of patients with advanced lung cancer have undergone transformatonal changes. The current paradigm for prescribing novel targeted therapies is based on selecting patients according to the presence of specific oncogenic abnormalities in the tumor. The efficacy of therapy targeted to a specific oncogene is the convincing evidence of ‘oncogene addiction’, or the concept that some cancers rely on or are ‘addicted to’ a specific gene for their survival and proliferation [1]. The first such abnormalities discovered in lung cancer were EGFR receptor (EGFR) kinase domain mutations, and tumors with these mutations were found to have sensitivity to EGFR tyrosine kinase inhibitors (TKIs) [2]. The echinoderm microtubule-associated protein-like 4 (EML4)—anaplastic lymphoma kinase (ALK) fusion has emerged as the second most important driver oncogene in lung cancer and the first targetable fusion oncoprotein to be identified in 4–6% of lung adenocarcinomas [3,4]. Crizotinib, an oral small molecule inhibitor of ALK and c-Met receptor kinases, is now approved for the treatment of ALK-positive advanced non-small-cell lung cancer (NSCLC), based on the results of two pivotal studies [5–7].

**EGFR NSCLC patients: second-line therapy & beyond**

A recent meta-analysis of patients with NSCLC and activating mutations in the EGFR showed that first-generation EGFR TKIs, such as gefitinib and erlotinib, significantly delayed disease progression but had no effect on overall survival (OS) [8]. Since the introduction of erlotinib and gefitinib, patients with metastatic EGFR-positive lung cancer can be offered a therapeutic alternative that has proven its superiority over standard platinum-based chemotherapy [2,9]. In the EURTAC study, in which erlotinib was compared with platinum-doublet chemotherapy as first-line treatment for patients with EGFR-mutant NSCLC, erlotinib demonstrated a significant improvement in the overall response rate (ORR) and median progression-free survival (PFS) [2]. On the basis of this study, in May 2013, the US FDA approved erlotinib for use in patients with lung cancers, harboring EGFR exon 19 deletions and EGFR L858R substitutions [2].

Primary or acquired resistance limits the therapeutic success of these targeted agents. Most such patients develop resistance to these drugs with progression of cancer after a...
median of 8–16 months. In the EURTAC trial, response was limited to 58% of the patients in the erlotinib group, and no impact on OS was observed [2]. Performance status or the presence of EGFR mutations in serum or plasma was also found to affect the outcome to EGFR TKIs [2]. PFS to erlotinib was 23.9 months for patients with PS0 compared with 8.8 months for patients with PS1 (p = 0.0006), while according to the presence or absence of EGFR mutations in serum or plasma, PFS was 11 and 8.4 months [2].

Among patients progressing to first-generation EGFR TKIs, 50% have tumors with a secondary T790M mutation [8]. T790M mutation is present in up to 62–82% of cases at the time of clinical progression to erlotinib [10,11]. The emergence of T790M EGFR gatekeeper mutation and upregulation of downstream signaling by mesenchymal–epithelial transition factor amplification have been described as the two main mechanisms responsible for acquired resistance [12]. Other mechanisms include EGFR amplifications, PIK3CA mutations or a transition from epithelial to mesenchymal differentiation. More interestingly, for a small percentage of resistant tumors, histological transformation occurs to small cell lung cancer [12].

At the same time, a consistent proportion of EGFR-mutant patients, approximately 30%, never respond to anti-EGFR TKIs due to primary resistance. The mechanism of this phenomenon is poorly understood. Deletion in exon 19 and L858R point mutation in exon 21 account for 90% of EGFR mutations detected in NSCLC and are clearly associated with benefit to EGFR TKIs [2]. The EGF-mediated phosphorylation of the Y845 tyrosine residue of EGFR is unique in the L858R missense mutant but not in the deletion mutant, which can partially explain their different sensitivity to EGFR activators TKIs through the activation of the STAT3/5 pathway [2,13]. ‘Uncommon’ EGFR mutations have a poorly understood clinical impact, and response rate, PFS and OS from gefitinib or erlotinib is not well defined [14]. Pre-existing T790M mutation was found in 27% of EGFR-mutant patients by massively parallel sequencing [15], in 31.5% by matrix-assisted laser desorption/ionization TOF mass spectrometry [11], in 35% by peptide nucleic acid (PNA) clamp real-time PCR (PCR–PNA assay) [16] and in 38% by the Scorpion Amplification Refractory Mutation System [17], and is related to shorter PFS to gefitinib or erlotinib [11,16,17].

In a H1975 xenograft tumor model, EGFR TKIs gefitinib and erlotinib did not significantly inhibit growth in vitro or in vivo [18]. However, significant tumor regression was observed using the VEGF monoclonal antibody bevacizumab or the combination of bevacizumab and erlotinib [18]. As proof of concept, the ongoing European Phase II BELIEF trial (NCT01562028) is examining the efficacy of erlotinib plus bevacizumab in patients with EGFR-mutant NSCLC stratified according to the presence of the T790M mutation [19]. Finally, it is worth mentioning that low BRCA1 levels neutralize the negative effect of the T790M mutation and are associated with longer PFS to erlotinib, indicating that the levels of BRCA1 can influence response to EGFR TKIs and the combination with PARP inhibitors can be superior to EGFR TKIs monotherapy [16].

Second-generation ‘irreversible’ EGFR TKIs
There is a need for second-generation ‘irreversible’ EGFR TKIs that can inhibit the T790M mutation. We have recently evaluated the frequency and potential impact of pretreatment EGFR T790M mutations in 95 patients with EGFR-mutant NSCLC included in the EURTAC trial using a PCR–PNA assay, and T790M mutations were detected in 65.26% of patients [20]. Currently, there are two lead second-generation EGFR TKI candidates, afatinib (BIBW2992) and dacomitinib (PF0299804), which maintain activity against EGFR mutations that have become resistant to erlotinib or gefitinib [21]. Whereas reversible EGFR TKIs compete with ATP in the kinase domain of EGFR, second-generation EGFR TKIs also compete for ATP binding but then covalently bind at the edge of the ATP-binding cleft on Cys773 of EGFR via the Michael mechanism (addition of nucleophile to an α, β unsaturated carbonyl) [22]. However, although afatinib and dacomitinib have been introduced to overcome acquired resistance, they showed limited efficacy in NSCLC with T790M and were more than 100-fold less potent in NSCLC cells with EGFR T790M mutation than in NSCLC cells with EGFR-activating mutation [23].

Afatinib inhibits both EGFR and human epidermal receptor 2 (HER2), while dacomitinib is a pan-HER inhibitor (EGFR, HER2, HER4). Afatinib has been studied in the LUX-Lung clinical trial program as both first-line treatment for patients with EGFR-mutant lung cancers and as treatment in the EGFR TKI acquired resistance setting [24]. The approval of afatinib was based on the demonstration of improved PFS in the multicenter, international, open-label, randomized LUX-Lung 3 trial. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio: 0.58; 95% CI: 0.43–0.78; p = 0.001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n = 308) was 13.6 months for afatinib and 6.9 months for chemotherapy [25]. After the recent FDA approval (12 July 2013) of afatinib monotherapy for the treatment of EGFR TKI-naïve patients with locally advanced or metastatic NSCLC with activating EGFR mutations, the European Commission has also granted marketing authorization (25 September 2013) for afatinib monotherapy for the same group of patients.

Dacomitinib (PF00299804) is a pan-HER family, orally active inhibitor that has activity toward EGFR, HER2 and HER4. Dacomitinib is being now compared with gefitinib in the Phase III ARCHER 1050 trial in patients with EGFR-activating mutations. The study was initiated on the basis of the data obtained in a single-arm Phase II trial (AT471017) of dacomitinib as first-line treatment for advanced NSCLC including a cohort of patients with EGFR-activating mutation. Of the 53 participants identified
with EGFR-activating mutations, 74% remained progression free at 1 year and nearly all patients were progression free at 4 months, the primary endpoint of the study and the preliminary median PFS for that group of 46 patients was 17 months [26].

In a H1975 tumor xenograft model, afatinib substantially inhibited tumor growth, while treatment with gefitinib produced only a marginal effect on tumor growth. However, the sensitivity of EGFR mutation-positive NSCLC cells to the antiproliferative effect of afatinib is reduced by the presence of the T790M mutation [27]. Therefore, many studies are trying to examine the value of combinatorial therapy targeting specific resistance pathways and mainly the T790M mutation. As happens with erlotinib, the combination of afatinib with bevacizumab has been found to be superior to either drug alone in a H1975 xenograft model harboring the T790M mutation [28]. In NSCLC cells with T790M mutation, afatinib inhibits EGFR phosphorylation and induces downregulation of thymidylate synthase. Combination therapy with afatinib and pemetrexed has an enhanced antitumor effect on the H1975 cells, while the combination of gefitinib and pemetrexed manifests an antagonistic interaction [27].

De novo resistance to afatinib or dacomitinib in NSCLC harboring EGFR T790M can occur through activation of JAK1/STAT3 signaling pathway via autocrine production of IL-6 in response to these drugs or through supply of IL-6 from tumor microenvironment in paracrine manner. Several agents targeting the IL-6R/JAK/STAT3 signaling pathway, such as IL-6 neutralizing monoclonal antibodies or STAT3 or JAK inhibitors, may be suitable candidates for combined therapy with irreversible EGFR TKIs (Figure 1) [23].

Akt kinase-interacting protein1 (Aki1) may be a critical mediator of survival signaling from mutant EGFR to Akt and may therefore be an ideal target for EGFR-mutant lung cancer patients, especially those with acquired EGFR-TKI resistance due to EGFR T790M gatekeeper mutation [29]. Aki1 knockdown further augments the inhibitory effect of afatinib and reduces viability of H1975 cells. Currently, a drug delivery system for Aki1 siRNA and small compounds with Aki1 inhibitory activity are under development (Figure 1) [29].

CO-1686 is a novel covalent inhibitor that irreversibly and selectively targets both the initial activating EGFR mutations as well as the T790M secondary acquired resistance mutation [30]. To investigate its use as a single agent, CO-1686 is being...
induced apoptosis of BCR–ABL leukemic cells. Interestingly, the neo host major effect of TKIs in sensitive EGFR-mutant cell lines is the induction of apoptosis. Interestingly, the BH3-only proapoptotic protein BIM mediates imatinib-induced apoptosis of BCR–ABL leukemic cells [34]. Kinase-driven cancers, including EGFR-driven NSCLC, maintain a survival advantage by suppressing BIM transcription and by targeting the BIM protein for proteasomal degradation through MAPK-dependent phosphorylation (Figure 1) [1]. AKT or MAPK inhibitors or chemotherapy can abrogate such events and induce apoptosis through activation of FOXO3 and its targets including BIM [1]. BIM expression is regulated by the MAPK pathway, which can be cross-regulated by the cAMP pathway, as shown by the inhibition of the RAF1 kinase by protein kinase A, a main effector of cAMP. Upregulation of the tumor-promoting factors PDE4A and PDE4D in lung cancer impairs cAMP generation through cAMP hydrolysis, activating the MAPK pathway [1]. Thus, the use of PDE4 inhibitors, which are used to treat asthma and chronic obstructive pulmonary disease, warrants further investigation in conjunction with EGFR tyrosine kinase inhibitors in EGFR-mutant NSCLC [1].

Recently, it was reported that BIM regulation is MAPK dependent, but independent of TORC1 and that BIM upregulation alone is not sufficient to promote maximal amounts of apoptosis [35]. Combining vemurafenib with a Bcl-2 inhibitor could abrogate tumor growth in melanoma-resistant cell lines with high levels of BIM, probably through releasing autophagic programmed cell death [36]. A mechanism of mTOR-dependent drug resistance, similar to BRAF-mutant melanomas, can be active in EGFR-mutant NSCLC that quickly develops resistance to gefitinib or erlotinib and adding an mTOR or a Bcl-2 inhibitor to treatment can block drug resistance and kill the cancer cells [35].

There are several causes that can lead to mTOR activation. For instance, AMP-activated protein kinase plays a central role in the control of cell growth, proliferation and autophagy through the regulation of mTOR activity, which is consistently deregulated in cancer cells, while loss of LKB1 prevents AMP-activated protein kinase activation in response to metabolic stress and induces mTORC1 activity [36]. Furthermore, diacylglycerol kinase-α regulates mTOR transcription via a unique pathway involving cyclic AMP, and diacylglycerol kinase-α is a central signaling hub and a promising therapeutic target [19].

Upon activation of mesenchymal–epithelial transition by its ligand HGF, which is provided by stromal cells, EGFR signaling becomes dramatically altered. HGF confers EGFR TKI resistance and at the same time induces interreceptor crosstalk with integrin β-4 (ITGB4), EphA2, CDCP1, Axl and JAK1. Heterodimerization between EGFR and the alternate binding partners may provide an alternative signaling mechanism for EGFR, thereby circumventing TKI inhibition [37]. Activation of NF-κB through silencing of IkB (also known as NFKBIA) can rescue EGFR-mutant lung cancer cells from EGFR TKI treatment and NF-κB or AXL, a receptor tyrosine kinase that activates NF-κB, could be potential companion drug targets, together with EGFR, in EGFR-mutant lung cancers and provides insight into the mechanisms by which tumor cells escape from oncogene dependence [38].

Furthermore, a transcriptional network involving the tumor suppressors Krüppel-like factor 6 and forkhead box O1 (FOXO1) negatively regulates activated EGFR signaling in both cell culture and in vivo models [39]. Targeted reduction of FOXO1 in the H1650 cell line confers drug resistance to erlotinib treatment that can be overcome through the rational combination of an FDA-approved drug – trifluoperazine hydrochloride, which is a FOXO1 nuclear export inhibitor, and erlotinib (Figure 1) [39].

Also, the potential therapeutic benefits of combining targeted inhibitors and immune modulation to improve patient outcomes should be investigated [40]. It has been described that BRAF-mutant melanoma cells resistant to BRAF inhibitors can have, through activation of the c-Jun and STAT3 pathway, increased expression of PD-L1 [40]. We can similarly speculate that the molecular resistance to EGFR or ALK inhibitors, as exemplified by increased MAPK signaling, prompts PD-L1 expression via enhancing the activity of c-Jun and its cofactor, STAT3. This can be an important basis for future clinical investigative strategies for combination of small molecules with immune checkpoint blockade to improve patient outcomes.

ALK NSCLC patients: second-line therapy & beyond

The novel ALK fusion is formed by a rearrangement occurring on the short arm of chromosome 2 and involves the
N-terminal portion of the EML4 protein and the intracellular signaling portion of the AKT tyrosine kinase receptor [41]. EML4–ALK generates a transforming tyrosine kinase with as many as nine different variants identified [42]. Patients with EML4–ALK-positive tumors are characteristically younger, female and never to light smokers [42]. The fusion gene has been observed predominantly in adenocarcinomas (4–7%) [42]. ALK-dependent mitogenic signaling is largely mediated via Ras/MAP kinase pathway as well as ALK-driven phosphatidylinositol 3 kinase activation. JAK/STAT3 pathway also provides essential survival signals and modulates cellular metabolism regulating the mitochondrial oxidation chain. STAT3 is activated by ALK either directly or through JAK (FIGURE 2) [43].

A recent Phase I trial of crizotinib achieved an objective response rate of 57%, a disease control rate of 87% at 8 weeks and a median PFS of 10 months [5,7]. On the basis of its safety and efficacy, crizotinib was granted accelerated approval by the FDA in August 2011 just 4 years after the discovery of ALK rearrangements in NSCLC [3]. In addition, a first-line Phase III trial comparing crizotinib and pemetrexed plus cisplatin is currently ongoing in ALK-rearranged NSCLC patients (NCT01154140). To ensure identification of patients who are most likely to benefit, the FDA approved crizotinib concurrently with a diagnostic test – the Vysis ALK Break Apart FISH Probe Kit – which has become the gold standard for detecting ALK rearrangements [44].

However, the success of a targeted drug is critically dependent on a sensitive and specific screening assay to detect the molecular drug target. The gold standard for detection of predictive ALK rearrangements is currently break-apart FISH, as it is able to detect all known ALK rearrangements and was clinically validated in crizotinib clinical trials [7]. However, the ALK FISH assay is fraught with technical challenges including FISH signal instability and scoring difficulties. The limitations of diagnosis with the use of FISH have been already reported by Chihara and Suzuki in 2011, making it clear that reconsideration of the diagnostic method is needed for further studies of ALK inhibitors [45]. Therefore, although ALK FISH is clinically validated, the assay can be technically challenging and other diagnostic modalities are being explored including immunohistochemistry and reverse transcriptase (RT)–PCR. Targeted resequencing has recently been proved as a promising method for ALK gene fusion detection in NSCLC, with results correlating significantly with those from FISH, RT–PCR and immunohistochemistry [46].

As happens with the majority of targeted agents, the tremendous excitement and enthusiasm that crizotinib sparked is tempered by the reality that a fraction of the target tumors is refractory from the start of treatment, and most patients will eventually relapse and become resistant after an initial response.

Resistance may frequently occur due to secondary mutations within the ALK kinase domain [47]. Among the 18 crizotinib-resistant patients examined for mutations in ALK that might underlie their resistance phenotype, Katayama et al. identified four (22%) with resistance mutations: three missense mutations (L1196M, G1202R, and S1206Y) and an amino acid (threonine) insertion mutation (1151Tins) [48]. The L1196M amino acid substitution is equivalent to gatekeeper mutations observed in EGFR (T790M) and BCR–ABL (T315I) that confer resistance to gefitinib and imatinib, respectively. Since these tumors are still addicted to ALK, considerable effort has focused on the development of second-generation inhibitors. Three such drugs are in clinical development, AP26113 (ARIAD Pharmaceuticals), LDK378 (Novartis) and alectinib (CH5424802/RO5424802, Chugai/Roche). LDK378 has shown high response rates in both crizotinib-naive and crizotinib-resistant patients with advanced NSCLC in a Phase I study, with an ORR of 57% for patients with prior
crizotinib and 60% in crizotinib-naïve patients [49]. Importantly, LDK is active in the CNS with durable responses observed [49]. Partial responses were observed in 75% of crizotinib-resistant ALK-positive patients, and one of the two crizotinib-naïve patients had a complete response in a Phase I/II study with Ariad’s AP26113, a second-generation ALK TKI that may also be active in patients with EGFR-mutant advanced NSCLC [50]. Alec tinib is a potent and specific investigational ALK inhibitor, which has recently been granted breakthrough therapy designation by the FDA in the USA. In a Phase I study performed in a Western population of 47 NSCLC patients who had failed to crizotinib, alecinib demonstrated an ORR of 59.5% and a median PFS of 3.1 months after more than 5 months follow-up. In addition, alecinib caused significant shrinkage of brain metastases, with only 4 of the 21 patients enrolled with pre-existing brain metastases having discontinued treatment due to disease progression [51,52].

One of the questions surrounding the second-generation ALK inhibitors is exactly how they will fit into the treatment landscape of ALK-positive NSCLC and if they stand a chance of outshining crizotinib at the frontline. Furthermore, encouraging early clinical results in NSCLC have demonstrated that ganetespib, a novel triazolone inhibitor of HSP90, may offer a potential strategy to target ALK inhibition for inducing substantial antitumor responses and overcoming acquired resistance in patients with ALK-positive lung cancer. When crizotinib was combined with ganetespib, crizotinib displayed superior antitumor efficacy compared with monotherapy in H3122 NSCLC xenografts [53].

Other ‘ALK-independent’ mechanisms, such as the activation of compensatory signaling pathways, may also confer resistance to targeted ALK agents. EGF-induced activation of EGFR, HER2 and HER3, as well as a reduced level of EML4-ALK activation, was associated with sustained downstream signaling in the presence of ALK inhibitors, indicative of a shift in survival dependency from the ALK signaling pathway to HER family pathways in the ALK-TKI-resistant cells [54]. The combination of an ALK inhibitor and an EGFR inhibitor induced apoptosis, further supporting the notion that the EGFR signaling pathway contributes to survival in cells resistant to ALK inhibitors (Figure 2) [54].

Finally, Takezawa et al. demonstrated that the expression of BIM and survivin are independently regulated by ERK and STAT3 signaling pathways, respectively, and that they are implicated in ALK–TKI-induced apoptosis in NSCLC cells positive for EML4-ALK [55]. A selective (and more potent than crizotinib) inhibitor of ALK kinase activity, NVP-TAE68, inhibits STAT3 phosphorylation and downregulates survivin in H2228 cells, but fails to inhibit ERK phosphorylation and upregulate BIM. In a recent study, the inhibition of both STAT3 and ERK pathways by the combination of TAE684 and a MEK inhibitor, AZD6244, was associated with a marked increase in the number of apoptotic cells [56].

Conclusion

TKIs are effective anticancer therapies, but resistance to these agents eventually develops. Several models of resistance to TKIs have been studied including resistance to EGFR inhibitors or ALK inhibitors. Clearly, the use of oncogene addicted, highly drug-sensitive cell line models to identify escape mechanisms should be one of our strategies for identifying and overcoming resistance. However, it is of paramount importance that when medically possible, we biopsy cancer recurrences in patients who become resistant to targeted therapies so that these mechanisms can be confirmed or refuted. By identifying how a patient’s cancer becomes refractory to targeted therapies, we will be well positioned to design rational treatment strategies to re-induce remissions. Only with expanding knowledge of these escape mechanisms, availability of drugs that therapeutically target escape pathways, and examples where such molecular data have informed a treatment decision resulting in good clinical outcome, can biopsy and molecular profiling of recurrent drug-resistant tumors may become widely practiced.

Expert commentary & five-year view

Currently, a great deal of research is being carried out which has begun to demonstrate, at the molecular level, the amount of histological and molecular heterogeneity inherent in NSCLC cells. Prospective studies have clearly demonstrated that certain specific mutations in EGFR tyrosine kinase or the presence of EML4–ALK translocation are associated with dramatic response to EGFR TKIs and crizotinib in patients with NSCLC. Nevertheless, the occurrence of clinical resistance limits the long-term results of these novel agents. Furthermore, knowledge of the molecular pathways and mutational drivers of lung cancer will expand the use of targeted treatments.

While we have made great advances, there still remains much to be done, and the identification of the molecular mechanisms responsible for acquired resistance to targeted therapy is crucial in order to pursue rational strategies to overcome resistance. Crosstalk between signaling pathways is a main mechanism of resistance. Identification of the molecular components involved could lead to the development of combination therapies cotargeting these molecules instead of EGFR tyrosine kinase or ALK inhibitor monotherapy. Additionally, novel biomarkers could be identified through deep sequencing analysis of serial rebiopsies before and during treatment and all of these efforts and knowledge can bring us closer to a more personalized approach to our patients’ care.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Key issues

- Translational research has described a newly clinically relevant molecular subset of nonsmall-cell lung cancer that is defined by EGFR (EGF receptor) mutations or echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (ALK) fusions.
- On the basis of theEURTAC study, the US FDA approved erlotinib for use in patients with lung cancers, harboring EGFR exon 19 deletions and EGFR L858R substitutions.
- Resistance mechanisms to EGFR inhibitors can be grouped into four categories: mutation of EGFR to a drug-resistant state (T790M); activation of a bypass signaling pathway; impairment of a pathway essential for apoptosis or autophagy and histological transformation to small cell lung cancer or an epithelial–mesenchymal transition.
- Crizotinib has become the gold standard for treating patients with ALK rearrangements.
- Resistance to crizotinib may frequently occur due to secondary mutations within the ALK kinase domain.
- Other ‘ALK-independent’ mechanisms, such as the activation of compensatory signaling pathways, may also confer resistance to targeted ALK agents.

References

Papers of special note have been highlighted as:

** of interest
** of considerable interest

** Rosell reviews the role of EGF receptor (EGFR) mutations, crosstalk between signaling pathways involved in intrinsic and acquired resistance and potential new clinical strategies.

** On the basis of this study, in May 2013, the US FDA approved erlotinib for use in patients with lung cancers harboring EGFR exon 19 deletions and EGFR L858R substitutions.
For personal use only.