Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor–Resistant Disease
Kadoaki Ohashi, Yosef E. Maruvka, Franziska Michor, and William Pao

ABSTRACT

Purpose
EGFR-mutant lung cancer was first described as a new clinical entity in 2004. Here, we present an update on new controversies and conclusions regarding the disease.

Methods
This article reviews the clinical implications of EGFR mutations in lung cancer with a focus on epidermal growth factor receptor tyrosine kinase inhibitor resistance.

Results
The discovery of EGFR mutations has altered the ways in which we consider and treat non–small-cell lung cancer (NSCLC). Patients whose metastatic tumors harbor EGFR mutations are expected to live longer than 2 years, more than double the previous survival rates for lung cancer.

Conclusion
The information presented in this review can guide practitioners and help them inform their patients about EGFR mutations and their impact on the treatment of NSCLC. Efforts should now concentrate on making EGFR-mutant lung cancer a chronic rather than fatal disease.

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INTRODUCTION

EGFR-mutant lung cancer was first described as a potential distinct clinical entity in 2004.1–3 Eight years later, multiple studies have undisputedly validated the disease as a unique subset of lung cancer, with its own clinical features, natural history, and clinical course. EGFR-mutant lung cancer also serves as a paradigm for an oncogene-addicted solid tumor that can be effectively treated with specific targeted therapy (ie, first-generation epidermal growth factor receptor [EGFR] tyrosine kinase inhibitors [TKIs], gefitinib [Iressa; AstraZeneca, London, United Kingdom] and erlotinib [Tarceva; Genentech, South San Francisco, CA]).4–8 Multiple reviews have been published on the rationale for targeting EGFR in cancer and the subsequent discovery of EGFR mutations in lung cancer.9,10 Here, we review new controversies and conclusions regarding the clinical implications of EGFR mutations in lung cancer, with a focus on EGFR TKI resistance.

DRUG-SENSITIVE EGFR MUTATIONS IN LUNG CANCER

EGFR is a receptor tyrosine kinase that belongs to the EGFR family, consisting of four members: EGFR, ERBB2, ERBB3, and ERBB4. Under normal circumstances, binding of ligands (eg, epidermal growth factor, transforming growth factor-alpha) activates the intracellular tyrosine kinase activity of EGFR via homo- or heterodimerization with EGFR family members.13 In lung cancer, EGFR mutations occur in exons encoding the ATP-binding pocket of the kinase domain (exons 18 to 21; Fig 1). In a cohort of nearly 1,200 patients with EGFR mutations linked to clinical outcomes, more than 145 different types of nucleotide changes have been reported within the EGFR kinase domain.14

The most clinically relevant and extensively studied drug-sensitive mutations are deletions in exon 19 that eliminate a common amino acid motif (LREA) and point mutations in exon 21 that lead to substitution of arginine for leucine at position 858 (L858R). Together, these two classes of mutations account for approximately 85% of EGFR mutations in the disease. They are constitutively active and oncogenic15,16 as a result of a disruption of autoinhibitory interactions.17 Biochemical studies indicate that these mutants preferentially bind to drugs like gefitinib and erlotinib over ATP.17,18 Other potential drug-sensitive mutations occur at much lower frequency: G719X (3%), L861X (2%),14 and exon 19 insertions (1%).19 The former two were associated...
with drug sensitivity in the original reports on EGFR mutations,\textsuperscript{1,2} whereas the exon 19 insertions were just recently reported as drug sensitive.\textsuperscript{19} The rarity of clinical data associated with these less frequent mutations has made it more difficult to determine how drug sensitive they are in patients, but new data are emerging.\textsuperscript{20,21}

**CLINICAL FEATURES ASSOCIATED WITH EGFR MUTATIONS**

EGFR mutations can be found in all histologic subtypes of non–small-cell lung cancer (NSCLC), including adenocarcinoma, large-cell carcinoma, and squamous cell carcinoma.\textsuperscript{14} In North American/European and East Asian countries, EGFR mutations are found in 10% and 30% of unselected NSCLCs,\textsuperscript{22,23} respectively. Clinical features likely to be associated with EGFR mutations include adenocarcinoma histology, history of never smoking cigarettes (ie, fewer than 100 cigarettes in a lifetime),\textsuperscript{22} and East Asian ethnicity.\textsuperscript{22} Female sex was originally thought to be correlated with EGFR mutations, but data suggest that this association was made because more women are likely to be never-smokers,\textsuperscript{24} not necessarily because of a true sex bias. Sixty percent to 80% of tumors from East Asian never-smokers with lung adenocarcinoma harbor EGFR mutations,\textsuperscript{25,26} whereas only 30% to 50% of tumors from North American/European counterparts have such mutations.\textsuperscript{3,22} The reason for this discrepancy is unclear; as of yet, no study has determined if US citizens of East Asian descent diagnosed with lung cancer have the same prevalence of EGFR mutations as East Asians themselves. Such a finding would suggest a genetic rather than environmental cause of EGFR alterations.

Most importantly, EGFR mutations (mostly exon 19 deletions and L858R point mutations) are associated with a clinical benefit from gefitinib and erlotinib. In early phase III trials, these drugs were tested in unselected patients with NSCLC and showed less than 10% radiographic response rates (RRs) with short (≤3 months) progression-free survival (PFS) rates\textsuperscript{27-29} (Table 1). After the discovery of EGFR mutations, several prospective single-arm first-line studies enrolling only patients with EGFR–mutant tumors reported unprecedented RRs (73% to 91%) and prolonged PFS (7.7 to 13.3 months).\textsuperscript{33} Thereafter, five large prospective phase III first-line trials directly compared an EGFR TKI versus platinum doublet chemotherapy in patients with NSCLC harboring EGFR mutations. These trials strongly confirmed the benefit of gefitinib or erlotinib in EGFR–mutant lung cancer, regardless of ethnic background (Table 1).\textsuperscript{4,6-9,30-32} By comparison,
patients with EGFR wild-type tumors displayed 1% RR and improved PFS with chemotherapy rather than a TKI. To receive EGFR TKIs in many regions, such as Canada and the European Union, patients must now have a documented EGFR mutation. In the United States, mutation testing is available in multiple molecular diagnosti- c laboratories certified by the College of American Pathologists and Certified Laboratory Improvements Amendment of 1988, but the US Food and Drug Administration (FDA) has never required that only patients with EGFR mutations should be treated with an EGFR TKI. The rationale behind this was that the BR.21 trial, which compared survival rates in unscreened patients with NSCLC treated with erlotinib versus placebo, showed a statistically significant survival benefit for patients taking the drug, even though the absolute difference was a mere 2 months (6.7 v 4.7 months; P < .001). However, consistent with the notion that erlotinib is more effective against EGFR-mutant tumors, a recent study reported that in patients with NSCLC harboring wild-type EGF, docetaxel induced a higher RR (13.9% v 2.2%; P = .004) and longer PFS (3.4 v 2.4 months; hazard ratio [HR], 0.69; P = .014) in the second-line setting than erlotinib.

**IMPACT OF EGFR TKIS ON EGFR-MUTANT LUNG CANCER**

No randomized prospective studies have yet officially shown that EGFR TKIs prolong overall survival (OS) compared with chemotherapy (Table 1). One explanation for this discrepancy is that once patients in the chemotherapy arm experience disease progression, they can still display high RR and prolonged PFS after switching to an EGFR TKI. This crossover confounds subsequent survival analyses.

However, several lines of evidence clearly show that patients with EGFR-mutant tumors and treated with TKIs experience historically high survival rates. Multiple prospective first-line clinical trials have now demonstrated that such patients live longer than 2 years. Such long OS was not routinely observed before the approval of EGFR TKIs (Table 1; Fig 2A). Consistent with these data, a retrospective analysis recently showed that OS in Japanese patients who started first-line chemotherapy after gefitinib was approved was much longer than the OS in patients who started chemotherapy before gefitinib approval (27.2 v 13.6 months; P < .001). Furthermore, although gefitinib was withdrawn from the market in the United States in 2005, approximately 250 patients with NSCLC were still alive as of 2011 in the AstraZeneca Iressa Expanded Access Program (NCT00034879), demonstrating that long-term survival of patients with NSCLC is possible while they receive EGFR TKIs.

The impact of the introduction of EGFR TKIs on the treatment of lung cancer can be further gleaned from an analysis of the US Surveillance Epidemiology and End Results (SEER) program database. Population-based resources like the SEER database do not include detailed information about patients by tumor mutation status. However, inferences can be made based on the frequency of patients with EGFR-mutant NSCLC among specific ethnic groups. For example, the 12-month survival rates for metastatic NSCLC from 1997 to 2008 of the three different ethnic groups represented in the SEER database (ie, white; African American; and Asian-Pacific Islander, Alaskan, and Native American) show that compared with predicted rates, there has been an increase in the survival rates of all groups. For Asians, the growth was larger than that of the other groups. This increase coincides with the widespread introduction of EGFR TKIs into the clinic;

 EGFR mutations and drug resistance

Unfortunately, approximately 30% of patients still do not experience disease responses despite harboring EGFR-mutant disease, and less than 5% experience a complete response (Table 1). Acquired resistance to EGFR TKIs in the metastatic setting is inevitable. Moreover, although the average PFS is 10 to 16 months, treatment duration can last as short as 1 month. Thus, drug resistance remains a major problem in the clinic. Until new therapies and strategies are developed to overcome such resistance, the new prevalence rate of lung cancer (Fig 2C) will remain flat. Here, we focus on mechanisms of primary and secondary resistance to EGFR TKIs.

**Primary Resistance**

*De novo resistant EGFR mutations.* Tumors with mostly EGFR exon 20 insertions, which account for 4% of EGFR mutations, are associated with a lack of drug sensitivity in preclinical models and in patients. Another mutation in exon 20 conferring resistance involves substitution of methionine for threonine at position 790 (T790M). This alteration is found as a heterozygous germline variant in 0.5% of never-smokers with lung adenocarcinoma and may confer genetic susceptibility to EGFR-mutant lung cancer. Efforts are being made to create an online registry of patients with germline EGFR T790M. When the T790M mutation occurs somatically, its frequency in EGFR TKI–naïve disease is somewhat controversial. Multiple studies have reported rarely detecting it pretreatment and mathematic modeling studies have suggested that pre-existing resistance may be present at a low frequency. Others have found frequencies as high as...
By contrast, the data are much more consistent in showing that more than half of patients with acquired resistance to gefitinib or erlotinib develop the T790M mutation. Patients whose tumors harbor somatic T790M mutations before treatment experience a shorter PFS.52,54 Suboptimal drug exposure. Suboptimal drug exposure may result in a lack of antitumor effect. In an interesting case report, disease in a patient with EGFR-mutant lung cancer (exon 19 deletion) progressed after only 2 months of erlotinib at the standard dose (150 mg orally once per day). The patient was found to have a low plasma concentration of drug, so the dose was increased. At 300 mg orally once per day, a significant response was achieved. Further investigation implicated a drug-drug interaction with fenofibrate. Erlotinib is extensively metabolized by the monoxygenase, cytochrome P450 3A4 (CYP3A4), which can be induced by fenofibrate. Subsequent withdrawal of fenofibrate led to suprahigh levels of erlotinib along with concomitant adverse effects, necessitating a reduction of erlotinib back to 150 mg orally once per day.55 How often such suboptimal dosing occurs is unknown. In an analogous manner, smoking has also been shown to affect erlotinib dosing through the upregulation of CYP1A1.56 Polymorphisms in the genes involved in erlotinib metabolism could further influence drug concentrations in individual patients, as seen with sunitinib in patients with renal cell carcinoma.57

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Failure of apoptosis induction. Induction of the proapoptotic BH-3-only molecule, BIM, is essential for apoptosis triggered by
EGFR kinase inhibitors in mutant EGFR–dependent lung adenocarcinomas both in vitro and in vivo.\textsuperscript{58} Low expression levels of BIM in primary tumors have been associated with shorter PFS in patients treated with EGFR TKIs.\textsuperscript{59} Functional variants of BIM that impair its function could also explain variability of response.\textsuperscript{60}

Other potential mechanisms. Other cell intrinsic factors may affect TKI sensitivity. Approximately 50% of NSCLCs, especially adenocarcinomas, harbor recurrent somatic alterations in genes that encode components of major signaling pathways, including ALK, ROS1, RET, HER2, KRAS, NRAS, PIK3CA, AKT1, BRAF, and MEK1.\textsuperscript{61-63} Among these, only PIK3CA mutations thus far have been shown to commonly co-occur with EGFR mutations.\textsuperscript{64} Introduction of PIK3CA into EGFR-mutant cells confers resistance to EGFR TKIs,\textsuperscript{46} and PIK3CA mutations have been shown to be acquired after patients develop resistance (Fig 3). The full spectrum of genome-wide genetic alterations associated with untreated EGFR-mutant lung cancer remains to be established. In another example, activation of the FAS/NFκB signaling pathway may modulate EGFR dependence in lung cancer cells (Fig 3).\textsuperscript{66} In this study, high expression of NFκB correlated with a significantly shorter PFS in patients treated with EGFR TKIs.

Exogenous factors may also affect EGFR TKI resistance in EGFR-mutant tumors. For example, in one study, hepatocyte growth factor (HGF), the ligand of the MET receptor tyrosine kinase, was found to be overexpressed in 29% of primary resistant lung tumors with drug-sensitive EGFR mutations (13 of 45).\textsuperscript{67} This result suggests that activation of the MET signaling pathway through HGF stimulation might be associated with primary resistance as well as acquired resistance (Fig 3). In another example, inflammation has been implicated as a resistance mechanism via activation of the interleukin-6/JAK2/STAT3 pathway (Fig 3).\textsuperscript{68} In xenograft models, administration of an anti-interleukin-6 antibody restores drug sensitivity.

Secondary Resistance

As we have stated, all patients with metastatic EGFR-mutant lung cancer will eventually develop disease progression. For more than 60% of patients, a plausible mechanism of resistance has been identified (Fig 4). The key to these studies has been analysis of new tumor tissue after patients develop resistance.\textsuperscript{69,70} A practice which should be considered standard to help guide therapy. Here, we review known mechanisms observed in human lung tumors as well as potential mechanisms found in preclinical models.

Second-site EGFR mutations. Second-site EGFR mutations are the most frequent mechanism of acquired resistance to EGFR TKIs in lung cancer, found in more than 50% of patients. Among the reported mutations—L747S, D761Y, T790M, and T854A—more than 90% are composed of the T790M gatekeeper mutation\textsuperscript{11,69-72} (Figs 1 and 4). The T790M substitution alters proper binding of the drug to the ATP pocket of EGFR and/or restores the affinity for ATP versus drug back to the level of wild-type EGFR.\textsuperscript{18}

Suboptimal drug exposure in the brain. Up to 33% of patients with EGFR-mutant lung cancer treated with EGFR TKIs will experience disease progression in the CNS.\textsuperscript{73,74} Thus far, the second-site EGFR T790M mutation has been found in only four (13%) of 30 examined, a frequency far lower than that seen in peripheral organs.\textsuperscript{74-79} Concurrently, multiple studies have shown that the concentration of drug achievable in the brain is approximately 1% to 5% of the level found in the plasma.\textsuperscript{75,77,80} Presumably, the selection pressure for second-site mutations is thus different in the brain versus the periphery. In those patients who experience disease progression only in the brain but not in the rest of the body, brain metastasis treatment should be administered, but erlotinib at standard daily doses can be resumed after completion of the radiation course. In the setting of leptomeningeal disease, which has been historically difficult to treat with conventional chemotherapy, high-dose EGFR TKI has
been shown to be clinically tolerable and potentially of some benefit with no dose-limiting toxicity. Such a dosing regimen leads to higher levels of drug in the cerebrospinal fluid (CSF; gefitinib 1,250 mg once per day: serum, 3,730 nmol/L and CSF, 39.4 nmol/L; erlotinib 1,500 mg orally once per week: plasma, 11,300 nmol/L and CSF, 130 nmol/L). Whether plasma drug concentrations decrease over time when EGFR TKIs are taken at standard doses remains unclear. In chronic myelogenous leukemia, studies have shown that imatinib levels can decrease the longer patients receive the drug.

Activation of EGFR signaling pathways via other aberrant molecules. Another 5% to 10% of cases of acquired resistance will display amplification of the gene encoding MET. Overexpression of MET activates the PI3K/AKT pathway via interaction with ERBB3, rendering cells less solely dependent on mutant EGFR for survival. In a tumor cell population, HGF may help expand pre-existing minor populations of cells harboring MET amplification (Figs 3 and 4).

Other mutant signaling proteins may also confer resistance. Up to 5% of patients with acquired resistance examined in one study developed new PIK3CA mutations. In another study of nearly 200 tumor samples from patients with acquired resistance, we recently found that approximately 1% of patients harbor BRAF mutations. No common mutations in KRAS, NRAS, or MEK1 signaling genes were detected. We have also recently shown that ERBB2 amplification may be associated with acquired resistance, especially in patients without detected T790M mutations. Other studies have suggested that CRKL or ERK amplification may be a mediator of disease progression.

Histologic transformation. In a handful of cases, rebiopsy of growing tumors has obtained cells that no longer display adenocarcinoma histology. Although they still harbor a drug-sensitive EGFR mutation, the cells display features of small-cell lung cancer or epithelial-to-mesenchymal transition (EMT). How cells transform to a different histology is not well understood. The RB and p53 pathways may have a role in the transformation to small-cell cancer, and the TGFβ pathway may play a role in EMT. In preclinical models, cells with EMT features seem to be no longer dependent on EGFR signaling for survival, but drug sensitivity may be restored by treatment with histone deacetylase inhibitors or inhibition of the kinase AXL or the zinc finger protein Slug.

### Strategies to Overcome Resistance

To overcome EGFR TKI resistance, several new drugs or drug combinations are being developed. To date, however, no agents have been approved for either the first-line setting or patients with acquired resistance.

**Second- and third-generation EGFR TKIs.** Second-generation EGFR TKIs include canertinib, neratinib, afatinib, and dacomitinib (Table 2). These irreversible ATP-competitive agents make covalent bonds with a cysteine residue at position 797 in EGFR. They are more potent than gefitinib and erlotinib and also affect other EGFR family members (eg, ERBB2, ERBB4). However, they still inhibit EGFR drug-sensitive mutations at lower concentrations of drug as compared with the common T790M mutant and therefore eventually select for cancer cells with EGFR T790M in preclinical models. In humans, the concentration of drug needed to overcome T790M-mediated resistance may be not achievable in the absence of significant toxicity.

Among these four drugs, afatinib has progressed the farthest in development. In a phase III trial for TKI-naive patients with EGFR-mutant tumors, afatinib was superior to platinum doublet chemotherapy in terms of RR (56.1% vs 22.6%; P < .001) and PFS (11.1 vs 6.9 months).

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**Fig 4.** Mechanisms of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Multiple mechanisms have been elucidated in human samples and preclinical models. Some factors may overlap. HGF, hepatocyte growth factor; IL-6, interleukin-6.
EGFR TKI-Resistant Disease

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Irreversible

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Third-generation

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Other

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Abbreviations: EGFR, epidermal growth factor receptor; EU, European Union; FDA, US Food and Drug Administration; MTD, maximum tolerated dose; NA, not applicable; NSCLC, non–small-cell lung cancer; TKI, tyrosine kinase inhibitor; VEGFR2, vascular endothelial growth factor receptor 2.

*Currently, no additional trials are being planned for lung cancer.
†XL647 inhibits EGFR, ERBB2, VEGFR2, FLT-4, and EPHB4.
‡Vandetanib failed to show a survival benefit in unselected patients after prior therapy with EGFR TKI.35 showed efficacy equivalent to that of erlotinib in unselected patients treated with one prior antitumor therapy for advanced NSCLC.36 showed an additive effect with docetaxel in unselected patients treated with one prior anticancer therapy for advanced NSCLC.37 The FDA has approved vandetanib as an RET inhibitor for medullary thyroid cancers under the trade name Caprelsa (AstraZeneca, London, United Kingdom).
§The FDA has approved lapatinib as an ERBB2 inhibitor for breast cancers. Dose was reduced to 240 mg orally once per day during trial because of toxicity.
¶AP26113 is reported to reversibly inhibit ALK and EGFR mutant proteins, including EGFR T790M.

In a separate randomized phase IIb/III trial of afatinib versus placebo for patients who “had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib”100(p529) (not necessarily with EGFR-mutant tumors), RR and PFS were 7% versus 1% and 3.3 versus 1.1 months, respectively.100 OS was 10.8 months in the afatinib arm and 12.0 months in the placebo arm.100 In a phase II trial, dacomitinib also has shown promising results in patients with untreated EGFR-mutant tumors (RR, 74%; preliminary median PFS, 17 months).101

Third-generation EGFR inhibitors include WZ4002102 and CO-1686.103 Whereas first- or second-generation EGFR TKIs have a quinazoline core, WZ4002 has an anilinopyrimidine core, which fits better into the ATP pocket of EGFR T790M. The structure of CO-1686 has not yet been released publicly. Notably, these reagents were designed to specifically inhibit the EGFR T790M mutant. To date, no clinical trials for WZ4002 have been initiated, but a phase II clinical trial for CO-1686 started in January 2012 (NCT01526928). Another new EGFR inhibitor is AP26113. This drug was originally characterized as an ALK inhibitor but has also been shown in preclinical models to inhibit EGFR mutants including EGFR T790M.104 A phase II clinical trial for AP26113 began in September 2011 (NCT01449461).

Drug combinations. Several studies have examined the addition of an anti-EGFR antibody to an EGFR TKI to overcome resistance. The combination of erlotinib with cetuximab showed no effect in patients who acquired resistance to EGFR TKIs (RR, 0%).12 However, the combination of afatinib and cetuximab has led to highly promising results (RR, 36% in eight of 22 patients).105 Results from this trial importantly demonstrate in patients that tumors remain dependent on EGFR signaling for survival even after developing resistance. Interestingly, 50% of the responders to this combination did not harbor EGFR signaling for survival even after developing resistance. Interests, 50% of the responders to this combination did not harbor EGFR TKI-resistant disease.

Other trials have assessed the combination of EGFR TKIs with other classes of inhibitors (eg, mammalian target of rapamycin inhibitors, SRC inhibitors, HSP90 inhibitors, and so on), but results have been disappointing.12 If there is no universal Achilles’ heel in tumors, specific combinations may need to be directed against the genetic makeup of individual tumors (eg, adding a MET inhibitor for tumors displaying no EGFR T790M but MET amplification, or adding a PI3K inhibitor for tumors displaying a secondary PI3KCA mutation, and so on).65,83.
Treatment beyond progression. Finally, recent preclinical and clinical studies have revealed interesting properties of EGFR TKI–resistant tumors. In standard practice, cytotoxic cancer drugs are usually discontinued when acquired resistance develops. However, many reports have demonstrated that patients who acquire resistance can respond to EGFR TKIs after a drug holiday.106 Multiple studies have now shown that patients who acquire EGFR T790M may have a favorable clinical outcome as compared with those who do not.97,107,108 Consistent with these findings, preclinical studies have demonstrated that cells that acquire EGFR T790M can actually grow slower than parental cells, and after several passages in the absence of TKIs, they become resensitized.51 These findings indicate that resistant tumors are composed of mixed populations of sensitive and resistant cancer cells and suggest a benefit of continued EGFR TKI administration even after the acquisition of resistance. Several clinical studies support this hypothesis,109-112 and prospective trials to test whether an EGFR TKI beyond progression is better than stopping the drug at the time of resistance are currently in progress (A Study of IRESSA Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone [IMPRESS]) as well as in development.

Novel combinations. Evolutionary mathematic cancer modeling in conjunction with in vitro experimental data was recently used to predict alternative dosing strategies that delay the outgrowth of preexisting resistance using currently available EGFR TKIs.51 The most promising strategy administers low-dose continuous EGFR TKI (eg, erlotinib) in combination with high-dose pulsed doses (eg, afatinib) with the goal of preventing both the replication of EGFR TKI–sensitive cells as well as optimally delaying the emergence of resistant clones. Such modeling also suggests that pulsed high doses alone will not be sufficient to suppress resistance. The clinical utility of this strategy should be validated. This integrated mathematic modeling and experimental approach represents a new roadmap for the rational design of clinical trials that can also be applied to other cancer types treated with targeted therapy.

Other novel combinations could involve TKIs plus immunologic therapies. BMS-936558 (MDX-1106), an antibody against programmed death-1, a T-cell inhibitory receptor, has shown promising activity in lung cancer with minimal toxicity.113 Addition of agents like BMS-936558 to erlotinib in TKI-naive patients or potentially with more potent TKIs after the development of resistance should be explored.

In conclusion, EGFR mutations define a distinct clinical entity of lung cancer. EGFR TKIs such as gefitinib and erlotinib have increased the OS of patients with EGFR-mutant lung cancer. However, despite rapid progress over the past 8 years, a new plateau for survival of patients with EGFR-mutant lung cancer already seems to have been reached. Greater efforts need to be made not only to overcome acquired resistance but also to induce greater responses and longer PFS in the first-line setting. The goal should now be to become as creative as possible with new strategies and therapies to make EGFR-mutant lung cancer a chronic rather than fatal disease.

REFERENCES

EGFR TKI–Resistant Disease


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Appendix

**Database Source**

