New Strategies in Overcoming Acquired Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer

Geoffrey R. Oxnard¹, Maria E. Arcila², Juliann Chmielecki², Marc Ladanyi², Vincent A. Miller*², William Pao³

¹Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
²Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY
³Vanderbilt-Ingram Cancer Center, Nashville, TN

*Corresponding author: Vincent A. Miller, MD
Thoracic Oncology Service, Department of Medicine
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY
Phone: 212-639-7243
Fax: 212-794-4357
Email: millerv@mskcc.org

Supported in part by the National Cancer Institute (P01-CA129243, R01-CA121210, U54-CA143798) and by a Young Investigator Award from the American Society of Clinical Oncology
Abstract

The management of non-small cell lung cancer (NSCLC) has been transformed by the observation that lung adenocarcinomas harboring mutations in EGFR are uniquely sensitive to EGFR tyrosine kinase inhibitors (TKIs). In these patients, acquired resistance to EGFR-TKI develops after a median of 10-14 months, at which time the current standard practice is to switch to conventional cytotoxic chemotherapy. Several possible mechanisms for acquired resistance have been identified, the most common being the development of an EGFR T790M gate-keeper mutation in over 50% of cases. In this review, we discuss recent advances in the understanding of acquired TKI resistance in EGFR-mutant lung cancer and review therapeutic progress with second generation TKIs and combinations of targeted therapies.
Background

EGFR-mutant lung cancer is a well-described molecular subgroup of lung adenocarcinoma characterized by a high prevalence in females, never-smokers, and Asians, and unique sensitivity to rationally targeted therapy with EGFR-TKI (1, 2). Patients with EGFR-mutant lung cancer develop disease progression after a median of 10-14 months on TKI (2, 3); no optimal therapy thereafter has yet been established.

Importantly, what defines acquired resistance is progression while receiving EGFR-TKI, irrespective of “line of therapy”. Rather, “TKI resistance” in EGFR-mutant lung cancer is a therapy-dependent clinical state, much like “castrate resistance” in prostate cancer (4). As in prostate cancer, one should ensure that patients are truly resistant before altering therapy. For example, patients who develop progression after having stopped TKI can still be sensitive to retreatment (5, 6), a phenomenon also described in GIST (7). Also, some patients can develop CNS-only progression, likely due to inadequate TKI penetration through the blood-brain barrier, and may still be sensitive to higher doses of TKI (8, 9); this “pharmacokinetic failure” has also been seen in ALK-mutant lung cancers treated with crizotinib, and such patients can continue to do well on TKI after receiving local therapy to the CNS (10). Including cancers which remain sensitive to erlotinib or gefitinib in clinical trials for acquired resistance could confound the interpretation of results.

As in castrate-resistant prostate cancer, there are indications that EGFR-mutant lung cancers maintain a degree of sensitivity to TKI despite development of acquired resistance. In a pilot study, Riely et al performed serial CT and PET imaging of patients with acquired resistance at three time points: before stopping TKI, after 3 weeks off TKI, and after 3 weeks of restarted TKI (11). Tumor volume and FDG avidity increased significantly after stopping TKI, and plateaued when TKI was restarted. In a separate series of patients discontinuing EGFR-TKI prior to enrolling in a clinical trial for acquired resistance, 22% developed accelerated progression (or “flare”) leading to hospitalization (12), occurring after a median of 8 days. Because of these clinical observations, our current practice is to...
continue erlotinib in patients with acquired resistance in addition to subsequent chemotherapies. This strategy is not yet the standard of care, but has led to a median survival of 33 months from start of TKI in one institutional cohort (13). A randomized trial studying post-progression erlotinib plus pemetrexed is ongoing, but eligibility is not limited to \textit{EGFR}-mutant cancers so the study may not accurately gauge the added value of continuing erlotinib with chemotherapy. A new randomized trial studying chemotherapy with or without erlotinib in \textit{EGFR}-mutant lung cancers with acquired resistance is under development.

One challenge for trials studying acquired resistance to EGFR-TKI is that tumor tissue is not always available to confirm the presence of a sensitizing \textit{EGFR} mutation. To ensure that these patients are not considered ineligible for trials in this setting, consensus clinical criteria for eligibility were recently published (14). These criteria note that patients who have had an objective response or durable stable disease (>6 months) to single-agent EGFR-TKI have a relatively high likelihood of harboring sensitizing mutations and could be considered eligible in addition to cases with known \textit{EGFR} mutations. However, the Jackman clinical criteria for acquired resistance have only a 66% positive predictive value for presence of an \textit{EGFR} sensitizing mutation, so molecular results should trump clinical criteria for eligibility at centers where mutation results are commonly available.

While multiple clinical trials have studied therapies for acquired TKI resistance, no published results have been practice-changing (Table). One limitation of these studies is varying definitions of acquired resistance and limited genotype data. Trials of single-agent second-generation TKIs (discussed below) have been disappointing. Trials combining erlotinib or gefitinib with targeted agents such as cetuximab, everolimus, and dasatinib have not demonstrated any objective responses (11, 15, 16). Lastly, though HSP90 inhibition showed some preclinical activity against xenograft models of TKI resistance (17), clinical trial results were discouraging (18). In the remainder of this review, we discuss emerging treatment strategies, focusing on those which could have the greatest promise in the future management of acquired resistance to EGFR-TKIs.
**On the Horizon**

**T790M-mediated acquired resistance**

At least half of *EGFR*-mutant tumors that develop TKI-resistance will harbor a second mutation in *cis* with the primary *EGFR* mutation (Figure 1) (19-21). The most common resistance mutation results from a threonine-methionine substitution at position 790 (T790M). T790M is analogous to the ABL T315I and KIT T670I "gatekeeper" mutations observed in imatinib-resistant CML and GIST, respectively (22, 23). Whereas most *EGFR* mutations are vulnerable to TKI because they decrease the receptor’s affinity for its natural substrate, ATP, the acquisition of T790M restores its affinity for ATP to wild-type levels, reducing the effect of TKI (24). Biochemical assays demonstrated that T790M confers synergistic kinase activity and transformation potential when expressed concurrently with a TKI-sensitive mutation (25, 26). However, despite this enhanced oncogenicity, T790M-harboring tumors in patients can display surprisingly slow rates of growth (27).

Multiple groups have modeled acquired resistance in vitro using *EGFR*-mutant NSCLC cell lines and increasing levels of TKI exposure. The resultant TKI-resistant cells harbor T790M and/or MET amplification, validating this approach as a useful *in vitro* tool for the study of clinically relevant acquired resistance mechanisms (25, 28-30). We have used a similar approach with erlotinib and the irreversible *EGFR* inhibitor BIBW2992 to derive T790M-harboring PC9 cells (carrying an *EGFR* exon 19 deletion). We observed a distinct growth disadvantage in T790M-containing cells versus their TKI-sensitive parental counterparts (Figure 2) (27). These differential growth kinetics may be partly responsible for the “flare” and “re-response” phenomenon (discussed above) observed in some patients with acquired resistance, and allow us to predict that resistant tumors are likely a mixed population of TKI-sensitive and -resistant cells. Upon withdrawal of the selective pressure (TKI), previously arrested TKI-sensitive cells can now repopulate more quickly than resistant cells, and tumors may regain sensitivity to TKI. Through evolutionary modeling based on these growth kinetics (27), we predict
clinical benefit to the continuation of TKI with chemotherapy in acquired resistance, as discussed above.

In patients with acquired resistance, T790M has also been found to be associated with a more indolent phenotype. We performed T790M testing on rebiopsy specimens from 93 patients with EGFR-mutant lung cancer and acquired resistance to TKI and found that those with T790M-mediated resistance had a better prognosis (31). Lack of T790M on rebiopsy was associated with a poorer performance status at progression, earlier development of new sites of metastatic disease, and shorter post-progression survival. The indolent nature of T790M-mediated resistance means that these patients can sometimes do well for months on continued single-agent TKI despite progression (32); the eventual development of more aggressive growth suggests a molecular “third hit”, the biology of which requires further characterization. The favorable prognosis associated with presence of T790M on rebiopsy suggests a valuable clinical role for rebiopsies in the management of these patients.

Detecting T790M in resistant tumors can be challenging due to limited tissue availability. Most lung cancers progress in areas that are not easily amenable to tissue sampling. Ideally, sampling procedures should be minimally invasive to reduce the risk of biopsy-related complications, but must still provide sufficient material for both morphologic and mutational analysis. In the MSKCC experience (20), small tumor samples obtained through minimally invasive procedures provided sufficient tissue in the majority of cases when adequately handled. Cell blocks prepared from malignant effusions can be a useful alternative to core biopsy in some patients. Prospective histologic/cytologic assessment is imperative in all cases to ensure adequate tumor content above the sensitivity level of testing method. For bone metastases, aspirates are preferable to core biopsies as these may provide higher tumor content and bypass the need for decalcification, which compromises DNA quality. Finally, the T790M mutation can also be detected in blood, either in DNA from circulating tumor cells or free plasma DNA (33, 34), but this remains a largely investigational approach at this time.
The establishment of high sensitivity testing methods is essential for accurate identification of the T790M mutation. Small tissue samples often preclude micro-dissection to enrich for tumor cells and thus may be vulnerable to false negative results. It has also been found that T790M can be present in a very low proportion of $\text{EGFR}$ alleles (30), and this allelic dilution can obscure detection of the T790M mutation. These factors mean that conventional Sanger sequencing is suboptimal for T790M testing in the acquired resistance setting. Higher sensitivity assays such as high performance liquid chromatography (HPLC), mass spectrometry, and locked nucleic acid-PCR techniques have been proposed as alternate methods (20, 35, 36). With high sensitivity assays, clinical laboratories must be unusually vigilant to guard against false positive results. For example, the DxS real time quantitative PCR assay for T790M was associated with false positive results, leading the manufacturer to remove this mutation from its panel (37).

Given that T790M-mediated resistance is the most prevalent mechanism of acquired resistance, multiple trials in this setting have attempted to target T790M (Table). In preclinical studies, irreversible EGFR-TKIs have been shown to effectively inhibit T790M-mutant cancers (38, 39). However, a phase II trial of neratinib showed little activity against $\text{EGFR}$-mutant lung cancers with acquired resistance to TKI, likely because toxicity limited administration of necessary dosing to attain therapeutic drug concentrations (40). In a phase II trial of PF00299804 after failure of erlotinib, no responses were seen in 7 patients with T790M-mutant NSCLC (41). In a phase III study of afatinib (BIBW2992) versus placebo given to 585 patients who progressed after $\geq 12$ weeks of TKI (42), overall survival (the primary endpoint) was equivalent in the two arms ($p=0.74$), though PFS was significantly prolonged with afatinib (median 3.3 months versus 1.1 months, $p<0.001$), with a 7% response rate. A new class of selective EGFR kinase inhibitors has recently demonstrated potent activity against T790M-mutant cell lines and mouse models; however these agents have not yet been tried in patients (43).

Another strategy for overcoming T790M-mediated resistance has been the addition of EGFR-targeted antibodies such as cetuximab, which may target EGFR in a different way than TKIs (44).
objective responses were seen when cetuximab was added to erlotinib in 13 patients with acquired resistance, but minor responses were seen in several patients (15). Mouse studies have examined what combination of EGFR-targeted therapies had maximal efficacy against T790M-harboring transgenic tumors and found that the combination of an irreversible TKI plus cetuximab effectively reduced tumor burden, while neither agent was effective alone (45). A phase Ib trial of afatinib plus cetuximab has now confirmed this activity in patients with acquired resistance, with a 40% objective response rate in 47 patients treated at the recommended phase II dose (46). These results validate preclinical data suggesting that many tumors are still addicted to the EGFR signaling pathway despite development of acquired resistance. To date, this has been the most promising approach in the treatment of patients with acquired resistance to EGFR-TKIs; PFS and overall survival results are eagerly awaited.

Other mechanisms of resistance

Another well-described mechanism of acquired TKI resistance relies upon increased signaling through MET, also a transmembrane receptor tyrosine kinase (29, 47). Coupling of MET to ERBB3 leads to sustained activation of the PI3K/AKT signaling pathway, bypassing the inhibited EGFR (29). In the initial studies, MET amplification was reported in up to 22% of acquired resistance cases, independent of T790M status. Two more recent studies each tested 37 patients for MET amplification by fluorescence in situ hybridization (FISH, Figure 1). One study found high amplification (MET:CEP7 ratio >3) in 1 case (3%) and lower level amplification (MET:CEP7 ratio 2-3) in 3 cases (in total, 11% amplified)(20); the second study reported 2 cases (5%) of high amplification (21).

The lower prevalence of MET amplification in these recent studies may be due to difficulty in identifying this genetic alteration in clinical specimens. The original studies used several methods to assess for amplification (29, 47), including array comparative genomic hybridization (aCGH), quantitative real-time PCR, and FISH. FISH is most widely available in clinical laboratories and requires only a single paraffin section. Importantly, both MET and EGFR are on chromosome 7, and polysomy
of chromosome 7 is common in NSCLC, particularly in those samples harboring EGFR mutations (48). Studies are needed to determine how best to distinguish clinically meaningful MET amplification and copy number gain from underlying polysomy, both in EGFR-mutant and wild-type lung cancers.

The efficacy of MET inhibition in the treatment of acquired resistance is not well-described. A phase I trial combining the MET inhibitor XL184 with erlotinib has been presented (49), and one patient with EGFR-mutant lung cancer had a confirmed partial response after progression on erlotinib alone. Another response was reported with the addition of ARQ197 to erlotinib for a patient that had progressed on the erlotinib arm of the first-line erlotinib with or without ARQ197 study (50); this patient harbored an EGFR mutation and elevated MET copy number. Recent data has suggested that a monoclonal antibody targeting MET (MetMAb), when combined with erlotinib, has activity against lung cancers with high MET protein expression (51), but neither this agent nor this biomarker have been assessed in cancers with acquired EGFR-TKI resistance.

A possible interaction between the EGFR/PI3K axis and DNA repair pathways represents a therapeutic opportunity that has not yet been pursued clinically. Cells with knock-down of the tumor suppressor gene PTEN, with constitutive PI3K activation, have been shown to have deficient homologous DNA repair and heightened sensitivity to PARP inhibition and cisplatin (52). Similar PI3K activation in EGFR-mutant lung cancer could explain the greater platinum sensitivity reported in this population when compared to EGFR wild-type cancers (3). Separately, erlotinib has been found to inhibit DNA repair in studies of breast cancer cell lines (53), an effect which could be potentiated in cells with deficient homologous DNA repair. Recent data has shown that patients with EGFR-mutant tumors and low BRCA1 levels gain a more durable benefit from erlotinib (median PFS = 27 months, p=0.02)(54). In light of this, trials are in development to assess the clinical activity of PARP inhibition in EGFR-mutant lung cancers with acquired resistance.

A handful of EGFR-mutant lung cancers have been found to exhibit histology consistent with small-cell lung cancer when biopsied after acquired resistance (20, 21, 55, 56). Five such cases were
recently identified from 37 studied (14%); all had adenocarcinoma at their baseline biopsy, all maintained a sensitizing \textit{EGFR} mutation at baseline and re-biopsy, and none of these resistant specimens also harbored T790M or \textit{MET} amplification. A lower prevalence was identified in the MSKCC experience, with 3 of 103 cancers with acquired resistance (3%) exhibiting either small cell or high grade neuroendocrine carcinoma on rebiopsy (20). Interestingly, pulmonary alveolar cells have also been found to occasionally transform to a small-cell morphology when loss of p53 and Rb1 is induced (57). Some have found that this histologic transformation is associated with sensitivity to platinum-etoposide combinations (21). Another morphologic change reported in some tumors with acquired resistance is epithelial-mesenchymal transition (21, 58), the therapeutic implications of which are unclear.

In conclusion, steady progress is being made in understanding the biology of acquired resistance to EGFR-TKI in \textit{EGFR}-mutant lung cancer and leveraging these understandings into rationally designed targeted and combination therapies. We predict that the relatively favorable prognosis of lung cancers harboring \textit{EGFR}-mutations means that patients with these cancers will gradually represent a larger proportion of the lung cancer population receiving treatment. As the prevalence of acquired resistance to EGFR-TKI grows, the importance of understanding the behavior and optimal management of these cancers becomes even more pressing. The most important initial steps remain clear: [1] wide-spread implementation of EGFR genotyping for lung adenocarcinoma, [2] understanding that these oncogene-addicted cancers require a distinct management paradigm, [3] improved utilization of rebiopsy tissue for molecular-typing of resistance, and [4] genotype-driven trials of rationally targeted therapies for patients with acquired TKI resistance.
Figure 1.

Frequency of acquired resistance mechanisms for EGFR-TKIs. Proportions are based on aggregate data from the two largest rebiopsy series to date, Arcila et al (n=99) and Sequist et al (n=37)(20, 21). MET amplification shown represents cases without co-existing EGFR T790M; another 3-4% of MET amplified cases also harbor the EGFR T790M. Small cell transformation group includes a case with non-small cell neuroendocrine differentiation. Not shown are other rare second site mutations in EGFR, one acquired PIK3CA mutation, and rare acquired beta-catenin mutations (both overlapping with EGFR T790M). Epithelial mesenchymal transition was studied in a small subset, so the prevalence is uncertain. Overall, there remain about one quarter to one third of cases for which the mechanism of acquired resistance is presently unknown.

Figure 2.

(A) Differential growth kinetics of isogenic EGFR-mutant TKI-sensitive (exon 19 deletion; blue) and -resistant (exon 19 deletion & T790M; red) cells. Data were derived from total cell counts of PC9 parental (sensitive) and PC9 resistant cells over 72 hours (27). (B) Schematic representing different treatment scenarios for EGFR-mutant lung cancer. Following initial treatment with an EGFR-TKI (e.g. gefitinib or erlotinib), EGFR-mutant tumors may shrink dramatically (blue cells; left). In most cases, progression is due to acquisition of the T790M mutation (red cells; middle). Upon cessation of TKI therapy, faster growing TKI-sensitive cells may repopulate (at times causing a “flare”), allowing the tumor to “re-respond” to a second round of TKI therapy following a drug holiday (right). If resistant tumors are indeed a heterogeneous mix of TKI-sensitive and -resistant cells (middle), continuation of TKI therapy along with chemotherapy following progression (bottom) will target both cell populations more effectively than chemotherapy alone (top). TKI: tyrosine kinase inhibitor
**Table:** Trials studying the efficacy of new therapies for acquired resistance to EGFR tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Phase</th>
<th>Key eligibility criteria</th>
<th># pts (%EGFRm)</th>
<th>Response rate, %</th>
<th>Efficacy, months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results published or in press</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riely, et al, CCR, 2007 (11)</td>
<td>Gefitinib or erlotinib &amp; everolimus (mTORi)</td>
<td>II</td>
<td>EGFRm &amp; SD x6m on TKI, or PR on TKI</td>
<td>13 (62)</td>
<td>0</td>
<td>3 (TTP)</td>
</tr>
<tr>
<td>Soria, et al, Ann Oncol, 2009 (59)</td>
<td>Everolimus (mTORi)</td>
<td>II</td>
<td>Prior TKI x1m</td>
<td>43 (0)</td>
<td>2</td>
<td>2.7 (TTP)</td>
</tr>
<tr>
<td>Sequist, et al, JCO, 2010 (40)</td>
<td>Neratinib (2gen TKI)</td>
<td>II</td>
<td>EGFRm and PR/SD x 3m on TKI</td>
<td>91 (100)</td>
<td>3</td>
<td>3.6 (PFS)</td>
</tr>
<tr>
<td>Sequist, et al, JCO, 2010 (18)</td>
<td>IPI-504 (HSP90i)</td>
<td>II</td>
<td>EGFRm and progressed on TKI</td>
<td>28 (100)</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Janjigian, et al, CCR, 2011 (15)</td>
<td>Erlotinib &amp; cetuximab (anti-EGFR mAb)</td>
<td>II</td>
<td>EGFRm, or PR/SD x 3m on TKI</td>
<td>19 (84)</td>
<td>0</td>
<td>3 (PFS)</td>
</tr>
<tr>
<td>Johnson, et al, JTO, 2011 (16)</td>
<td>Dasatinib (SRCi) or erlotinib &amp; dasatinib</td>
<td>II</td>
<td>EGFRm, or PR/SD x 6m on TKI</td>
<td>12 (100)</td>
<td>Dasatinib: 0 Both: 0</td>
<td>0.5 (PFS) 0.9 (PFS)</td>
</tr>
<tr>
<td><strong>Results presented</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller, et al, ASCO, 2008 (60)</td>
<td>XL647 (2gen TKI)</td>
<td>II</td>
<td>EGFR T790M, or PR/SD x 3m on TKI</td>
<td>23 (NR)</td>
<td>One PR in 8 evaluable pts</td>
<td>NR</td>
</tr>
<tr>
<td>Campbell, et al, ASCO, 2010 (41)</td>
<td>PF00299804 (2gen TKI)</td>
<td>II</td>
<td>KRAS wt and any prior TKI</td>
<td>66 (50)</td>
<td>5</td>
<td>4.5 (PFS) in EGFRm pts</td>
</tr>
<tr>
<td>Park, et al, ASCO, 2010 (61)</td>
<td>PF00299804 (2gen TKI)</td>
<td>II</td>
<td>KRAS wt and any prior TKI</td>
<td>42 (21)</td>
<td>15; 2 PR in pts with EGFRm</td>
<td>3.6 (PFS)</td>
</tr>
<tr>
<td>Wakelee, et al, ASCO 2010 (49)</td>
<td>Erlotinib &amp; XL184 (METi)</td>
<td>I/II</td>
<td>Unselected (most had prior TKI exposure)</td>
<td>54 (37)</td>
<td>8; 1 PR in an EGFRm pt</td>
<td>NR</td>
</tr>
<tr>
<td>Miller, et al, ESMO, 2010 (42)</td>
<td>Afatinib (2gen TKI) vs. placebo</td>
<td>III</td>
<td>PR/SD x 3m on TKI</td>
<td>390 (NR)</td>
<td>Afatinib: 7 Placebo: 0.5</td>
<td>3.3 (PFS) 1.1 (PFS)</td>
</tr>
<tr>
<td>Janjigian, et al, ASCO, 2011 (46)</td>
<td>Afatinib (2gen TKI) &amp; cetuximab (anti-EGFR mAb)</td>
<td>I/II</td>
<td>EGFRm, or PR/SD x 6m on TKI</td>
<td>47 (96)</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Trials in progress or results pending</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00503971</td>
<td>Erlotinib &amp; vorinostat (HDACi)</td>
<td>I/II</td>
<td>EGFRm and prior TKI x 3m</td>
<td>~50 planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00660816</td>
<td>Erlotinib &amp; pemetrexed vs. pemetrexed alone</td>
<td>II</td>
<td>Prior TKI x 3m</td>
<td>~78 planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00994123</td>
<td>Erlotinib &amp; MM-121 (anti-ERBB3 mAb)</td>
<td>II</td>
<td>EGFRm, or PR x 3m on TKI</td>
<td>~43 planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01121575</td>
<td>PF00299804 (2gen TKI) &amp; PF02341066 (METi)</td>
<td>I/II</td>
<td>PR/SD x 6m on TKI</td>
<td>~70 planned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01259089</td>
<td>Erlotinib &amp; AUY922 (HSP90i)</td>
<td>II</td>
<td>EGFRm, or PR/SD x 6m on TKI</td>
<td>~43 planned</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pts: patients, EGFRm: EGFR mutation positive, wt: wild-type, TKI: EGFR tyrosine kinase inhibitor, 2gen: 2nd-generation, mAb: monoclonal antibody, i: inhibitor, PR: partial response, SD: stable disease, TTP: time to progression, PFS: progression free survival, NR: not reported
References


EGFR T790M and rare second site mutations (60%)

MET amplification (4%)

Small cell transformation (6%)

Unknown* (30%)

*Includes epithelial-mesenchymal transition, present at an uncertain prevalence

CCR New Strategies
New Strategies in Overcoming Acquired Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer

Geoffrey R. Oxnard, Maria E. Arcila, Juliann Chmielecki, et al.

Clin Cancer Res  Published OnlineFirst July 20, 2011.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-10-2571

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.