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Maintained Sensitivity to EGFR Tyrosine Kinase Inhibitors in *EGFR*-Mutant Lung Cancer Recurring after Adjuvant Erlotinib or Gefitinib

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Abstract

Purpose: Given the unprecedented efficacy of EGFR tyrosine kinase inhibitors (TKI) in advanced *EGFR*-mutant lung cancer, adjuvant TKI therapy is an appealing strategy. However, there are conflicting findings regarding the potential benefit of adjuvant EGFR-TKI in patients with lung cancer harboring *EGFR* mutations. To better understand these results, we studied the natural history of lung cancers which recurred despite adjuvant TKI.

Experimental Design: Patients with recurrent *EGFR*-mutant lung cancer following adjuvant TKI were identified using an Institutional Review Board-approved mechanism. Recurrent cancer specimens were tested for resistance mutations. Sensitivity to retreatment with EGFR-TKI was evaluated.

Results: Twenty-two patients with cancers harboring an *EGFR* sensitizing mutation received adjuvant erlotinib or gefitinib for a median of 17 months (range 1–37 months). T790M was more common in cancers which recurred while receiving TKI than in those which recurred after stopping TKI (67% vs. 0%, $P = 0.011$). Fourteen patients who developed recurrence after stopping EGFR-TKI were retreated, with a median time to progression of 10 months and radiographic response seen in 8 of 11 patients with evaluable disease (73%).

Conclusions: Recurrence of *EGFR*-mutant lung cancer after stopping adjuvant TKI should not preclude a trial of TKI retreatment; a phase II trial of erlotinib in this setting is underway. Studies of adjuvant EGFR-TKI will underestimate the potential survival benefit of adjuvant TKI for patients with *EGFR*-mutant lung cancers if retreatment at recurrence is not given. *Clin Cancer Res; 17(19); 6322–8. ©2011 AACR.*

Introduction

The remarkable efficacy of EGFR tyrosine kinase inhibitors (TKI) against non–small cell lung cancers (NSCLC) harboring *EGFR* activating mutations has transformed lung cancer management. EGFR-TKIs like erlotinib and gefitinib are now a standard first-line therapy for patients with advanced lung cancer harboring *EGFR* mutations, after multiple randomized studies have confirmed their efficacy in this population (1–3). This success has led to investigations of whether erlotinib or gefitinib may have a role in early stage disease, to improve outcomes following definitive therapy.

Our group recently reported our experience using adjuvant TKI treatment in 167 patients with *EGFR*-mutant lung cancer and identified an improved 2-year disease-free survival (DFS) in patients who received perioperative EGFR-TKI (adjusted HR 0.53, $P = 0.06$) when compared with no adjuvant TKI (4). However, 2 prospective trials of adjuvant gefitinib delivered to unselected patients (i.e., both *EGFR* mutant and *EGFR* wild-type patients) have had disappointing results. A randomized study by the Southwest Oncology Group (SWOG) evaluated daily gefitinib maintenance following chemoradiation for stage III NSCLC and found that patients randomized to placebo lived a median of 14 months longer than those receiving gefitinib (5). More recently, results from the randomized placebo-controlled BR.19 study showed no survival benefit for adjuvant gefitinib (6). Neither of these studies selected for patients with tumors harboring *EGFR* mutations (7, 8). In the BR.19 study, where *EGFR* mutation status was tested post-hoc in a subset of patients, no survival benefit was identified for

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Translational Relevance

Adjuvant tyrosine kinase inhibitor (TKI) therapy for *EGFR*-mutant lung cancer is a biologically appealing treatment strategy; however, preliminary clinical data is conflicting. Although one large retrospective series has shown a disease-free survival benefit, a post-hoc analysis of a prospective trial of adjuvant TKI showed no survival benefit in the subgroup of cancers with *EGFR* mutations. In this analysis, we studied a cohort of patients with *EGFR*-mutant lung cancers which recurred after adjuvant EGFR-TKI, and we found that cancers which recur after TKI is stopped do not harbor the T790M resistance mutation and can commonly have durable responses to retreatment. Though it is not the convention in non–small cell lung cancer, patients with *EGFR*-mutant lung cancers which recur after stopping adjuvant EGFR-TKI should be offered subsequent retreatment. Furthermore, trials of adjuvant TKI may significantly underestimate the potential benefit of TKI treatment if retreatment at or after recurrence is not undertaken.

gefitinib over placebo (HR 1.58, $P = 0.16$) in 76 patients whose tumors harbored *EGFR* mutations (6). Several ongoing studies are prospectively evaluating whether selected lung cancer cohorts gain benefit from adjuvant erlotinib. One such study (RADIANT) has completed accrual after randomizing more than 900 patients to adjuvant erlotinib versus placebo, but only 12% of patients are known to have tumors harboring *EGFR* mutations (9).

Importantly, adjuvant therapy with TKIs has been also prospectively evaluated in the treatment of gastrointestinal stromal tumor (GIST), where adjuvant imatinib improved DFS when compared with placebo but did not prolong overall survival (OS; ref. 10). One hypothesis for why adjuvant TKI might improve disease free but not OS is that the TKI is merely delaying recurrence by suppressing the growth of residual disease after surgery, but not eradicating minimal residual disease. Thus, patients who do not receive adjuvant TKI may garner equal benefit by receiving TKI at recurrence. In a best case scenario, adjuvant TKI would eliminate minimal residual disease, preventing recurrence, and curing a subset of patients. In a worst case scenario, adjuvant TKI might alter the biology of the disease in such a way that the recurrent cancer is somehow more virulent or resistant to TKIs, thereby worsening survival. Understanding the characteristics of patients with recurrent cancer is one strategy for evaluating the effect of the adjuvant therapy on the disease.

Given the interest in adjuvant EGFR-TKI for treatment of lung cancer and the disappointing preliminary results from BR.19, we undertook an analysis of recurrent *EGFR*-mutant lung cancers to better understand the impact of adjuvant TKI. Specifically, we were interested in exploring the relationship between adjuvant EGFR-TKI and the development of the T790M second-site mutation, which is highly prevalent in advanced cancers which develop acquired resistance to TKI (11, 12). Preclinical data suggest that when an EGFR-TKI is stopped, *EGFR*-mutant cell lines which have acquired the T790M resistance mutation revert to T790M-negative after a period of time without TKI exposure (13), perhaps because the slow growing clones carrying T790M are overgrown by the parental *EGFR*-mutant cells. Analogously, we hypothesized that those cancers which recur after stopping EGFR-TKI would be sensitive to TKI retreatment.

Materials and Methods

Using an Institutional Review Board-approved mechanism, patients with recurrent *EGFR*-mutant lung cancer were identified from a database of patients who received adjuvant or neoadjuvant gefitinib or erlotinib (4, 14, 15). Because we have previously found that *EGFR* mutations are consistently present over the course of TKI treatment (12), patients were considered eligible for this analysis if an *EGFR* mutation could be identified either at diagnosis or at recurrence. Patients were excluded if they received "adjuvant" TKI for stage IV disease after having had metastectomy or some other attempt at definitive therapy.

Pathologic specimens from biopsies conducted following recurrence were studied for molecular characteristics of resistance, when available. *EGFR* genotyping was done using fragment analysis or mass spectrometry, as previously reported (16, 17). We tested for the T790M second-site mutation using a highly sensitive locked nucleic acid (LNA)-based PCR/sequencing assay which uses an LNA probe to suppress the amplification of wild-type DNA, and allows the preferential amplification of the T790M-mutant allele (12). *MET* FISH analysis was done to evaluate for *MET* copy number alterations when sufficient material was available (12).

Each patient's clinical course was reviewed and patients were divided into 2 groups: those who developed recurrence while receiving adjuvant TKI, and those who developed recurrence after stopping adjuvant TKI. Patients developing recurrence after stopping adjuvant TKI were further divided into those who stopped due to toxicity and those who stopped after completing a planned course of adjuvant TKI [often 24 months, the treatment course given as part of several adjuvant protocols (6, 9, 18)]. Date of recurrence was defined as the date of the suspicious imaging examination which led to biopsy or treatment for recurrence. Time to recurrence on adjuvant EGFR-TKI was defined as the time between the first dose of TKI (either neoadjuvant or adjuvant) and the date of recurrence. Time to progression (TTP) on TKI retreatment was defined as the period between restarting TKI and development of clinically determined disease progression. Time-to-event analyses were done using a Kaplan–Meier method. Probability comparisons were done using Fisher's exact test.

Table 1. Patient and treatment characteristics ($n = 22$)

	Characteristic	*n* (% total)
Age	Median (range)	61 (37–88)
Stage	I	5 (23)
	II	3 (14)
	III	14 (64)
Histology	Adenocarcinoma	22 (100)
EGFR sensitizing mutation	Exon 19 deletion	13 (59)
	Exon 21 L858R	8 (36)
	Exon 19 insertion	1 (5)
Definitive treatment modality	Surgery only	8 (36)
	Surgery and adjuvant chemotherapy	4 (18)
	Neoadjuvant chemotherapy	7 (32)
	Neoadjuvant chemoradiation	2 (9)
	Definitive chemoradiation	1 (5)
TKI timing	Neoadjuvant only	1 (5)
	Adjuvant only	17 (77)
	Neoadjuvant and adjuvant	4 (18)
TKI received	Gefitinib	6 (27)
	Erlotinib	16 (73)
Recurrence timing	While receiving TKI	7 (32)
	After completing TKI	15 (68)

Results

Sixty-five patients treated with adjuvant or neoadjuvant EGFR-TKI were identified from an institutional database of 222 patients with early stage *EGFR*-mutant lung cancer [the details of this cohort are being reported separately (15)]. Among these, the 22 patients who had developed disease recurrence were eligible for this analysis. The baseline and treatment characteristics of the 22 patients are shown in Table 1. Nineteen of the patients (86%) had an *EGFR* mutation detected in their primary tumor prior to adjuvant treatment; for the remaining 3 patients, baseline testing was not available but an *EGFR* mutation was identified at recurrence. Patients were started on neoadjuvant/adjuvant EGFR-TKI between 8/03 and 4/09, and received TKI for a median of 17 total months (range 1–37 months). Seven patients (32%) developed recurrence while receiving adjuvant TKI and 15 patients (68%) developed recurrence after having stopped adjuvant TKI. Of the 15 patients who developed recurrence after stopping TKI, 7 (47%) completed a planned course of therapy (median 25 months on TKI) and 8 (53%) stopped due to intolerance (median 5 months on TKI).

Recurrence characteristics

The median time to recurrence on EGFR-TKI was 25 months for the entire cohort. Median time to recurrence was 16 months in patients who developed recurrence on TKI, 15 months in patients who stopped TKI due to intolerance, and 39 months in patients who completed a planned course of adjuvant TKI therapy. In all patients who stopped TKI, the median time off TKI until relapse was 13 months (range 1–48 months). All but one of the patients who developed recurrence while taking TKI had stage III disease (86%), while approximately half of the patients who developed recurrence after stopping TKI had stage III disease (53%, $P = 0.19$). Recurrence in the brain tended to be more common in patients who had stopped TKI (40% vs. 0%, $P = 0.12$; Table 2), while recurrence only in lung and lymph nodes tended to be more common in patients receiving TKI (86% vs. 47%, $P = 0.16$).

Eighteen of the 22 patients had a biopsy confirming recurrence and 15 of these were adequate for molecular studies. An *EGFR* sensitizing mutation could be identified in 14 of the 15 specimens; 1 patient with a history of resected stage IIIA disease harboring an *EGFR* exon 19 deletion subsequently underwent resection of a mediastinal lymph node which was found to be *EGFR* wild type. In retrospect, an additional *EGFR* wild-type primary was identified in the initial resection specimen from this patient, potentially explaining the wild-type recurrence. T790M was detected in 4 of the 14 specimens harboring an *EGFR* sensitizing mutation (29%). T790M was common in cancers which recurred on TKI (67%, 95% CI: 22%–96%; Table 2) but was not detected in any of the cancers which recurred after TKI was stopped (0%, 95% CI: 0%–34%, $P = 0.011$). *MET* FISH results were available for 6 specimens, and increased copy number was seen in 1 biopsy from a cancer which recurred on TKI.

Efficacy of TKI retreatment

Of the 15 patients who developed recurrence after stopping EGFR-TKI, 14 received TKI retreatment following

Table 2. Recurrence characteristics by subgroup

	Recurred while receiving TKI	Recurred after stopping TKI	*P*
Patients	$n = 7$	$n = 15$	
Recurrence in lung and/or lymph nodes only	6 (86%)	7 (47%)	0.16
Recurrence in CNS	0 (0%)	6 (40%)	0.12
Specimens with genotyping	$n = 6$	$n = 9$	
EGFR sensitizing mutation detected at recurrence	5 (83%)[a]	9 (100%)	0.40
EGFR T790M detected at recurrence	4 (66%)	0 (0%)	0.011

[a]One patient had a synchronous *EGFR* wild-type primary identified, believed to explain the *EGFR* wild-type recurrence.

recurrence (Table 3); the remaining patient received chemotherapy elsewhere. Radiographic response was seen in 8 of 11 patients (73%, 95% CI: 39%–94%) with evaluable disease (Supplementary Fig.); the other 3 patients had no evaluable disease due to radiation or metastectomy. Median TTP on TKI retreatment was 10 months and median survival was 23 months (Fig. 1). Of the 4 patients with TTP of 3 months or less on TKI retreatment, all had CNS involvement at time of recurrence, with 2 of these patients recurring less than 3 months after stopping adjuvant TKI therapy. One patient who developed progression on TKI retreatment subsequently underwent a tumor rebiopsy; while T790M had not been present in the initial recurrence specimen, acquired T790M was detected in the rebiopsy done after progression while receiving erlotinib for advanced disease.

Discussion

In this analysis of patients with *EGFR*-mutant lung cancers which recurred despite adjuvant EGFR-TKI therapy, we have found that patients who develop recurrence after stopping TKI are unlikely to harbor a detectable T790M mutation and can have durable responses to TKI retreatment. This is in contrast to the convention in NSCLC, where patients who have recurrence after adjuvant cytotoxic chemotherapy are commonly believed to be refractory to the adjuvant drugs which were used, such that retreatment is avoided. Our data indicate that retreatment with EGFR-TKI should be considered in patients with *EGFR*-mutant lung cancer who develop recurrence after stopping adjuvant TKI, and may allow them to garner substantial therapeutic benefit from such agents.

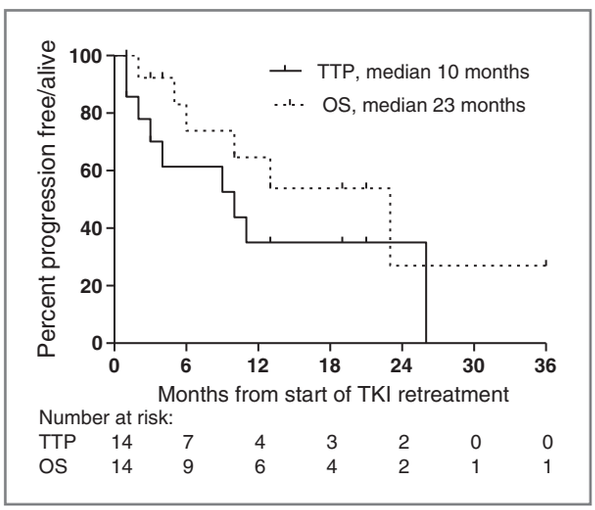

Figure 1. TTP and OS from start of TKI retreatment, in patients who develop a recurrence of *EGFR*-mutant lung cancer after stopping adjuvant TKI. A portion of patients gain durable disease control on TKI despite prior adjuvant exposure.

Our findings are consistent with our improved understanding of acquired resistance to TKIs in *EGFR*-mutant lung cancer. In studies of *EGFR*-mutant cell lines, it has been found by multiple groups (11, 12, 19) that exposure to EGFR-TKI will, with time, lead to the acquisition of a secondary T790M mutation which restores EGFR phosphorylation in the presence of TKI. More recently, it has been shown that withdrawal of TKI from cell lines and patients with acquired resistance leads to gradual loss of the T790M mutation (13, 20), such that sensitivity to EGFR-TKI is reacquired. This phenomenon may be due to indolent growth of T790M-mutant cells (13), leading to overgrowth by parental cells harboring only the *EGFR* sensitizing mutation, or due to *EGFR* alleles lying in extra-chromosomal double-minutes which can be lost from cells without appropriate selection pressure (21). Our clinical dataset supports these preclinical findings—while micrometastases that survive adjuvant EGFR-TKI treatment may acquire T790M, this mutation is not detected after a period of TKI withdrawal, perhaps due to the slow growth of these clones. This indolent phenotype of T790M-mutant cells may also explain the trend toward a lower incidence of CNS recurrence in cancers that recurred while on TKI, since T790M-mediated acquired resistance has been found to be associated with later development of new metastatic disease sites (22). Interestingly, a similar finding of later brain metastasis has also been described in advanced *EGFR*-mutant lung cancer treated with TKI therapy (23, 24).

Our findings have potentially important implications for the future study and use of adjuvant TKI therapy in *EGFR*-mutant lung cancer. When considering the impact of

Table 3. Efficacy of retreatment with an EGFR-TKI for patients who developed recurrence after having stopped adjuvant TKI

Adjuvant TKI, mo	Reason TKI stopped	Interval off TKI, mo	Recurrent sites	Response to TKI retreatment?		TTP, mo
29	Completed	2	Brain, liver, bone, lung	No:	Progressive liver metastases	1
25	Completed	8	Brain	NE:	NED after brain metastectomy	>19
25	Completed	12	LN	Yes:	Response in LN, consolidated with radiation	26
27	Completed	13	Pleura, LN	Yes:	Durable PET response, though CT stable	>16
23	Completed	15	Brain, CSF, bone	NE:	Symptomatic decline, thought to be due to CNS radiation	1
20	Completed	21	Lung	Yes:	Resolution of multiple ground-glass opacities	>3
22	Completed	21	CSF, bone	NE:	Durable control of irradiated CSF disease	10
6	Toxicity	1	Brain	No:	Progression in the brain	2
6	Toxicity	4	Lung, bone	Yes:	CR of 1 cm lung nodule, symptomatic bone response	11
6	Toxicity	5	Brain, lung	No:	Progressive brain metastases	3
1	Toxicity	11	Lung, LN	Yes:	Major response in lung and LN	9
3	Toxicity	15	Lung	Yes:	Brief response in lung, but erlotinib stopped due to toxicity	4
4	Toxicity	30	LN, bone	Yes:	Early response in LN	>1
19	Toxicity	48	Lung	Yes:	Durable CR in lung nodules	>13

NOTE: Nine of the above patients had recurrent tissue available for mutation testing; all harbored a sensitizing mutation, and none harbored a T790M comutation.

Abbreviations: CR, complete response; CSF, cerebrospinal fluid; LN, lymph node; NE, nonevaluable.

adjuvant TKI, it is worth restating that the aim of adjuvant therapy in solid tumor oncology is to improve OS by eradicating minimal residual disease following definitive therapy. Historically, therapies with shown efficacy against advanced cancer have been subsequently evaluated in the adjuvant setting, leading to the successful development of adjuvant doxorubicin for breast cancer, fluorouracil for colon cancer, and cisplatin-based chemotherapy for NSCLC. Targeted therapies have also had success in the adjuvant setting: trastuzumab improves OS after resection of HER2 positive breast cancer (25), while adjuvant imatinib improves DFS for resected GIST (10), and may also improve OS in high risk populations (26). However, the addition of bevacizumab to adjuvant chemotherapy did not significantly improve DFS in resected colon cancer (27), while adjuvant bevacizumab remains under investigation in NSCLC (28).

There are several possible reasons why an adjuvant-targeted therapy could fail to improve OS, the simplest being that the therapy may have inadequate antitumor effect. In the case of adjuvant EGFR-TKI, one could hypothesize that the subset of lung cancers which recur after adjuvant TKI are those that were refractory to this targeted agent due to the *de novo* presence of resistance mutations. However, this study suggests that recurrent cancers infrequently harbor known resistance mutations and often show the expected sensitivity to TKIs seen in advanced *EGFR*-mutant lung cancers. A second explanation for why adjuvant-targeted therapy may fail to improve survival is that it has deleterious effects, either on the patient or on the tumor biology. Patient toxicity is one reason why cytotoxic chemotherapy is avoided in resected stage IA NSCLC where any positive impact on survival may be outweighed by potentially dangerous side-effects (29). Alternatively, a harmful effect on tumor biology, leading to increased invasiveness, has been suggested to explain why adjuvant bevacizumab fails to improve survival in the treatment of resected colon cancer (27, 30, 31).

Regarding adjuvant EGFR-TKI, the SWOG study of gefitinib following chemoradiation for patients with stage III NSCLC found no increase in toxic death rate among patients randomized to gefitinib (5). Although patients on the gefitinib arm had a trend toward a shorter progression-free survival (PFS; 8 vs. 12 months, $P = 0.17$), these patients were not selected on the basis of *EGFR* genotype and no genotyping from this trial has ever been reported. For BR.19, the available data does not include an analysis of DFS in the subset of patients with cancers harboring *EGFR* mutations, but a concerning incidence of toxic deaths from gefitinib was not identified (6). Thus, there is no clear

indication that gefitinib fails as an adjuvant therapy for *EGFR*-mutant lung cancer due to toxicity or hastening progression, a conclusion supported by the published series showing a better DFS for *EGFR*-mutant lung cancer patients who had received adjuvant TKI (4).

We propose that there may be an additional reason why an active adjuvant therapy could fail to improve survival: specifically, by impacting subsequent treatment patterns without directly affecting disease biology. In the conventional management of recurrent NSCLC, agents given in the adjuvant setting are generally avoided because of the anticipated resistance. For small cell lung cancer, NCCN guidelines use duration of response as a marker of the value of retreatment (32), however, no such distinction is made for NSCLC (33). But avoidance of TKI retreatment after "failing" a course of adjuvant TKI could have a major impact on the apparent effectiveness of such an adjuvant strategy in clinical trials. For example, in the subset of 76 patients with *EGFR*-mutant lung cancer treated on the BR.19 study (6), those patients randomized to gefitinib, though intended to receive a full 24 months of TKI, received a median of only 5 months of treatment because the study was closed early (5). At the time of recurrence, patients who received adjuvant gefitinib (the study was unblinded when it was halted) may have received other therapies preferentially due to suspected resistance to TKI. In comparison, patients randomized to placebo would have been candidates for gefitinib or erlotinib following recurrence because both gefitinib and erlotinib were available for advanced NSCLC during the follow-up period. By receiving a full course of TKI until progression, these patients would have had a median time on TKI of 10 to 14 months (1, 34), and could have received TKI longer than patients on the adjuvant gefitinib arm of the study. In effect, patients with *EGFR*-mutant lung cancer who were randomized to adjuvant TKI could have been undertreated, receiving an abbreviated course of adjuvant treatment rather than treatment until progression following recurrence. Accurate interpretation of this aspect of the BR.19 trial results requires knowledge of whether patients randomized to gefitinib received subsequent TKI retreatment.

This analysis provides little insight regarding the optimal duration of adjuvant TKI therapy. Although patients who completed a planned course of adjuvant TKI seem to have had a longer median time to recurrence than those who stopped TKI early, there is significant bias in attempting such a retrospective analysis; the former group inherently has the most favorable natural history, while the latter group stopped TKI due to greater vulnerability to toxicity. However, we note that responses to TKI retreatment were seen both in patients who completed 2 years of adjuvant TKI and in those who stopped adjuvant TKI early (Table 3). Interestingly, while adjuvant cisplatin-based chemotherapy prolongs survival with just 3 to 4 months of treatment (35), no trial to date has studied the value of a few months of adjuvant TKI. The SWOG study of maintenance gefitinib planned a maximum of 5 years of therapy (5), the BR.19 study planned 2 years of adjuvant gefitinib (though was stopped early; ref. 6), and the RADIANT study is evaluating 2 years of adjuvant erlotinib (9). Because the BR.19 study was halted early, patients received varying durations of adjuvant TKI—it would be useful to study in this unbiased cohort whether duration of TKI therapy influenced DFS. In addition, future trials could consider studying a shorter course of adjuvant TKI for *EGFR*-mutant lung cancer, so long as retreatment with TKI is incorporated at recurrence.

The retrospective nature of our analysis precludes us from determining whether sensitivity to TKI at recurrence is in any way diminished due to the adjuvant TKI exposure. One could hypothesize that, though initially responsive to TKI, these recurrent cancers may have a hidden resistance mechanism which could be revealed after a short period of retreatment. Our data indicate, however, that durable responses can occur with TKI retreatment. A phase II study of erlotinib in this setting is currently ongoing (NCT01189435), with the aim of prospectively evaluating the response rate and PFS with TKI retreatment. We believe that adjuvant TKI therapy for *EGFR*-mutant lung cancer remains a potentially valuable treatment strategy deserving of future study, so long as future studies prospectively include recommendations for TKI retreatment in appropriate patients.

Disclosure of Potential Conflicts of Interest

Y.Y. Janjigian: commercial research grant, Boehringer-Ingelheim. G.J. Riely: consultant/advisory board, AstraZeneca, Boehringer-Ingelheim, Ariad, Chugai, and Tragara. W. Pao: commercial research grant, AstraZeneca, Enzon, and Xcovery; ownership interest, Molecular MD; consultant/advisory board, Molecular MD, AstraZeneca, Bristol-Myers Squibb, and Symphony Evolution. M.G. Kris: consultant/advisory board, Boehringer-Ingelheim and Pfizer. V.A. Miller: consultant/advisory board, Boehringer-Ingelheim Pharmaceuticals, OSI Pharmaceuticals, and Genentech. The other authors disclosed no potential conflicts of interest.

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