Impact on Disease-Free Survival of Adjuvant Erlotinib or Gefitinib in Patients with Resected Lung Adenocarcinomas that Harbor *EGFR* Mutations

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Background: Patients with stage IV lung adenocarcinoma and epidermal growth factor receptor (*EGFR*) mutation derive clinical benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs). Whether treatment with TKI improves outcomes in patients with resected lung adenocarcinoma and *EGFR* mutation is unknown.

Methods: Data were analyzed from a surgical database of patients with resected lung adenocarcinoma harboring *EGFR* exon 19 or 21 mutations. In a multivariate analysis, we evaluated the impact of treatment with adjuvant TKI.

Results: The cohort consists of 167 patients with completely resected stages I to III lung adenocarcinoma. Ninety-three patients (56%) had exon 19 del, 74 patients (44%) had exon 21 mutations, and 56 patients (33%) received perioperative TKI. In a multivariate analysis controlling for sex, stage, type of surgery, and adjuvant platinum chemotherapy, the 2-year disease-free survival (DFS) was 89% for patients treated with adjuvant TKI compared with 72% in control group (hazard ratio = 0.53; 95% confidence interval: 0.28–1.03; $p = 0.06$). The 2-year overall survival was 96% with adjuvant EGFR TKI and 90% in the group that did not receive TKI (hazard ratio: 0.62; 95% confidence interval: 0.26–1.51; $p = 0.296$).

Conclusions: Compared with patients who did not receive adjuvant TKI, we observed a trend toward improvement in DFS among individuals with resected stages I to III lung adenocarcinomas harboring mutations in *EGFR* exon 19 or 21 who received these agents as adjuvant therapy. Based on these data, 320 patients are needed for a randomized trial to prospectively validate this DFS benefit.

Key Words: Adjuvant therapy, Erlotinib, Gefitinib, EGFR mutation, Lung adenocarinoma.

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The most effective treatment for lung adenocarcinoma is complete (R0) surgical resection, with anatomical resection (lobectomy or pneumonectomy) as the preferred surgical procedure.[1] Nevertheless, even for patients who have complete resections, many are not cured, and rates of death 5 years after resection vary from 30% in stage IA to 75% in stage IIIA.[2] Perioperative cisplatin-based chemotherapy given before and/or after surgery can increase overall survival (OS) after non-small cell lung cancer (NSCLC) resection by treating occult metastatic disease.[3–6] Perioperative cytotoxic chemotherapy reduces the risk of death at 5 years by approximately 15% (absolute risk reduction) in patients with stage IIIA disease and approximately 4% for patients with stage IB NSCLC. For stage IA disease, despite the unacceptably high recurrence rate at 5 years, treatment with adjuvant cisplatin chemotherapy has no survival benefit.[7]

NSCLC is a heterogeneous disease, with activating mutations in epidermal growth factor receptor (*EGFR*) playing a key role in the growth and proliferation of approximately 20% of lung adenocarcinomas. Multiple prospective trials demonstrate that individuals with advanced lung adenocarcinomas that harbor *EGFR* mutations, deletions in exon 19, or L858R missense mutations at exon 21 experience a high rate of radiologic response with the EGFR tyrosine kinase inhibitors (TKIs) erlotinib (Tarceva) or gefitinib (Iressa).[8–11] Three randomized phase 3 trials demonstrated that gefitinib is superior to platinum-based chemotherapy as an initial treatment for advanced lung adenocarcinoma among patients with *EGFR* mutations, improving both radiologic response and progression-free survival.[12–14] The presence of

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EGFR mutations may be an independent, good prognostic factor in lung adenocarcinoma irrespective of therapy.[12,15–17]

Because EGFR TKIs are superior to cytotoxic drugs in patients with advanced lung adenocarcinoma and *EGFR* mutation, many have proposed that EGFR TKIs may also prove advantageous when used as adjuvant treatments in this population. As such, our institution routinely tests all resected lung adenocarcinomas for the presence of *EGFR* mutations. This has allowed our participation in ongoing, prospective clinical trials of EGFR TKIs for patients with *EGFR* mutations (NCT00567359). It also affords the opportunity to observe the clinical outcome of patients who received adjuvant EGFR TKIs outside of a clinical trial. To accomplish this, we reviewed a prospectively maintained surgical database that includes clinical and molecular characteristics and outcome data for patients with resected stages I to III lung adenocarcinoma with *EGFR* mutations.

PATIENTS AND METHODS

Patients

In an institutional review board-approved surgical database, we identified all patients with completely resected stages I to III lung adenocarcinomas with *EGFR* mutations who had a resection at Memorial Sloan-Kettering Cancer Center (MSKCC) between May 2002 and August 2008. Some of these patients received EGFR TKIs gefitinib or erlotinib pre and/or postoperatively as routine care or under the auspices of a clinical trial of perioperative gefitinib.[18] The surgical database prospectively captures patient sex, age, type of surgery, histology, pathologic stage, perioperative chemotherapy, and radiation. From the medical record, we obtained the information regarding erlotinib or gefitinib delivery, disease status, and survival. This review of records was done under a waiver of authorization approved by the MSKCC Institutional Review Board and Privacy Board. According to the consensus of MSKCC surgeons and medical oncologists, patients at MSKCC are followed up for disease recurrence in uniform fashion, including a doctor visit and computed tomography scan of the chest (preferably with IV contrast) every 6 months until the 2-year anniversary of the date of surgery and noncontrast computed tomography annually thereafter.

EGFR Mutation Testing

Since January 2006, *EGFR* mutation testing has been performed reflexively (automatically) at MSKCC by the molecular diagnostic core laboratory of the Department of Pathology on all resected lung adenocarcinomas. DNA is extracted from formalin-fixed, paraffin-embedded tumor tissue and tested by a polymerase chain reaction-based assays for the two predominant types of *EGFR* mutations—short in-frame deletions in exon 19 and a specific point mutation in exon 21 at codon 858 (L858R) (methods described in Ref. 19). Before 2006, mutation testing was done on many, although not all resected patients using a variety of techniques, including direct sequencing. Using direct sequencing, tumors from two patients were found to have a point mutation in exon 21 at codon 861 (L861Q), which is also associated with sensitivity to erlotinib and gefitinib.[20–22]

Statistical Analysis

The characteristics of patients who received neoadjuvant and/or adjuvant TKI were summarized and compared with the group that did not receive TKI using Wilcoxon rank sum test or Fisher's exact test. Disease-free survival (DFS) was measured from date of surgery to date of recurrence or death. OS time was measured from date of surgery to date of death. Living patients were censored at the date of last contact. Survival data were obtained using the medical record and the Social Security Death Index. Survival status was updated in March 2010. Survival probabilities were calculated by the Kaplan-Meier method and compared among different groups using the log-rank test. Univariate and multivariate Cox regression analyses were performed controlling for sex, stage, surgical procedure, and perioperative platinum-based chemotherapy. Perioperative erlotinib or gefitinib therapy was treated as a time-dependent factor, so that when it was given after the surgery, its effect would not be taken into account until the start of the therapy. Statistical analyses were done using SAS (SAS Institute, Inc., Cary, NC) software.

RESULTS

Patient Characteristics

We identified 167 patients with stages I to III completely resected lung adenocarcinomas harboring *EGFR* exon 19 or 21 mutations that underwent resection at MSKCC between May 2002 and August 2008. The demographic characteristics of the patients are summarized in Table 1. The cohort consists predominantly (70%) of stage I resected lung adenocarcinomas, such that only 47 patients (28%) in the

TABLE 1. Patient Demographic and Baseline Characteristics

Characteristics	Adjuvant Erlotinib/ Gefitinib ($N = 56$)	No Adjuvant Erlotinib/ Gefitinib ($N = 111$)	p
Age (yr)			
Median	66	70	0.050[a]
Range	37–88	35–89	
Sex, no. (%)[b]			
Male	15 (27)	31 (28)	1.00
Female	41 (73)	80 (72)	
Pathologic stage, no. (%)			
I	30 (54)	87 (78)	0.002
II	11 (20)	14 (13)	
III	15 (27)	10 (9)	
Cisplatin chemotherapy, no. (%)	22 (39)	23 (21)	0.016
Surgery type, no. (%)			
Bilobectomy	3 (5)	0	0.010
Lobectomy	49 (88)	91 (82)	
Pneumonectomy	1 (2)	0	
Segmentectomy	1 (2)	9 (8)	
Wedge	2 (4)	11 (10)	

[a] p value calculated using Wilcoxon rank sum test. Other p values calculated using Fisher's exact test.

[b] Percentages may not sum to 100 because of rounding.

entire cohort received perioperative cisplatin-based chemotherapy. Fifty-six patients (33%) received perioperative erlotinib or gefitinib. The adjuvant erlotinib/gefitinib group had a higher proportion of stage III patients. Stage distribution among the group is summarized in Table 1. Twenty-one of the adjuvant TKI-treated patients captured by the database were enrolled in a phase 2 clinical trial and received perioperative gefitinib consisting of induction therapy for 21 days before surgery and again postoperatively for up to 2 years.[18] The remaining 35 patients received postoperative erlotinib or gefitinib at the discretion of their physicians. The median time between start of erlotinib/gefitinib therapy and surgery was 2 months. The median time on erlotinib or gefitinib was 20 months (range, 0.3–51 months).

TABLE 2. Characteristics of Patients Who Recurred or Died

Characteristics	Adjuvant Erlotinib/Gefitinib (N = 13)	No Adjuvant Erlotinib/Gefitinib (N = 43)
Age (yr)		
Median	62	68
Range	38–88	35–85
Sex, no. (%)[a]		
Male	6 (46)	13 (30)
Female	7 (54)	30 (70)
Pathologic stage, no. (%)		
I	3 (23)	30 (70)
II	4 (31)	5 (12)
III	6 (46)	8 (19)
Cisplatin chemotherapy, no. (%)	7 (54)	10 (23)

[a] Percentages may not sum to 100 because of rounding.

Survival Analysis

To date, a total of 46 recurrences (27%) and 29 deaths (17%) have occurred. Ten patients died without documented disease recurrence. Table 2 summarizes the characteristics of patients who recurred or died. Of the patients who recurred, 43 developed unresectable metastatic disease: eight brain/leptomeninges only, 15 lung/pleura only, and 20 recurrences in multiple disease sites: brain, bone, lung, liver, or lymph nodes. Three patients were rendered free of disease recurrence in the lung with surgery. These tumors were all histopathologically similar to the primary resection specimens with identical *EGFR* mutations, excluding a second primary lung tumor as a possibility.

In the entire cohort of completely resected stages I to III lung adenocarcinoma harboring *EGFR* mutations, the median OS and DFS of all patients were 76 months (95% confidence interval [CI]: 71 to not reached) and 46 months (95% CI: 40–67), respectively. Kaplan-Meier survival estimates are provided in Figure 1. In a multivariate analysis, after adjusting for sex, pathologic stage, surgery type, and application of cisplatin-based chemotherapy, patients treated with perioperative erlotinib/gefitinib therapy had a 2-year DFS rate of 89% compared with 72% for patients who were not treated with perioperative erlotinib/gefitinib (p = 0.06), presented in Table 3. Of the 46 patients who experienced disease recurrence, 32 (69%) received EGFR TKI therapy for recurrent disease, one patient was rendered disease free with resection and is being monitored off therapy, three patients died without

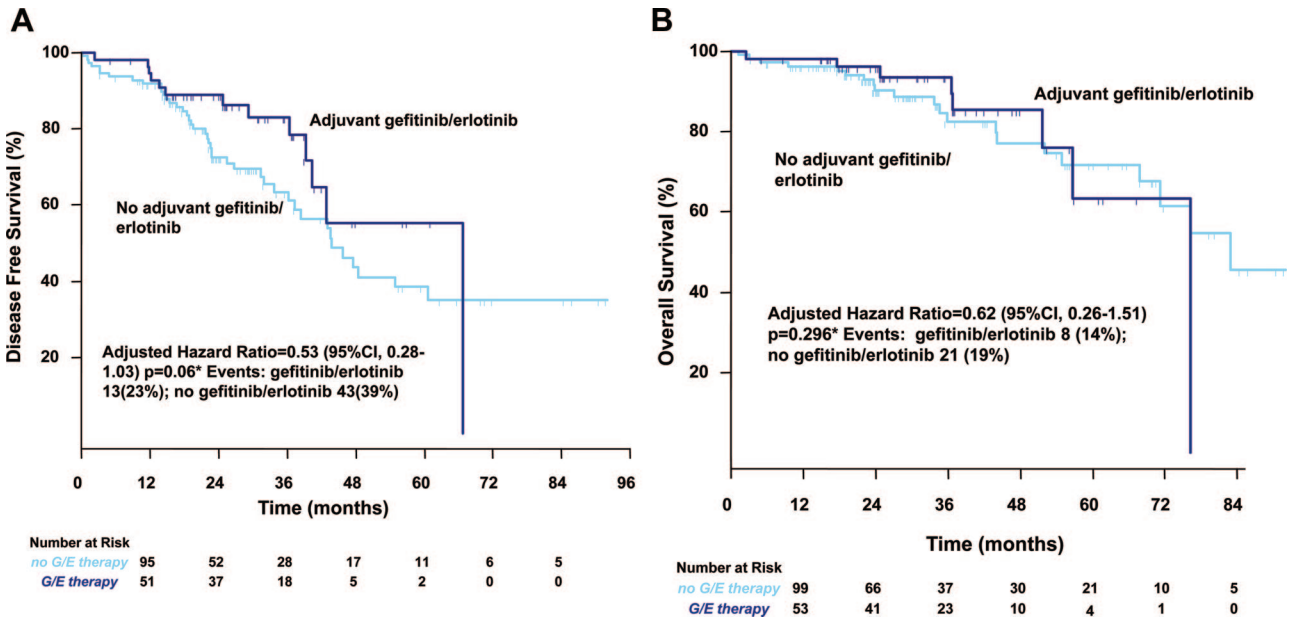

FIGURE 1. Kaplan-Meier curves for survival. Kaplan-Meier curves for disease-free survival (panel *A*) and for overall survival (panel *B*) by gefitinib/erlotinib therapy. G/E denotes gefitinib/erlotinib. *Hazard ratios were calculated with the use of a Cox proportional hazards model, with the type of surgery, stage, cisplatin chemotherapy, and sex as covariates and gefitinib/erlotinib therapy as time-dependent factor; Cox proportional hazards model with gefitinib/erlotinib therapy as time-dependent factor. With respect to the disease-free survival and overall survival, results of a log-rank test, p = 0.122 (panel *A*) and p = 0.912 (panel B).

TABLE 3. Multivariate Disease-Free Survival Analysis

n = 167	*N* (Event *N*)	2-yr Survival (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Adjusted *p*
Adjuvant erlotinib/gefitinib	56 (13)	89% (77–95)	0.53 (0.28–1.03)	0.06
No adjuvant erlotinib/gefitinib	111 (43)	72% (61–80)		

[a] Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.
CI, confidence interval.

receiving erlotinib or gefitinib, and for 10 patients, the therapy for metastatic disease is unknown. In a multivariate analysis, patients treated with perioperative erlotinib/gefitinib had a 2-year OS of 96% compared with 90% for patients who were not treated with perioperative erlotinib/gefitinib ($p = 0.296$), presented in Table 4.

DISCUSSION

In advanced lung adenocarcinoma, the response rates to EGFR TKI therapy in patients with *EGFR* mutations range from 58 to 75% in prospective trials.[9–12,15,23–25] Three randomized phase 3 studies have demonstrated that EGFR TKI therapy is superior to chemotherapy in this unique subset of patients with advanced NSCLC.[12–14] If we assume that patients with micrometastatic disease after surgery would have a similar benefit, we can hypothesize that adjuvant EGFR TKI could delay relapse or potentially cure patients with resectable cancer who would otherwise relapse with adjuvant cisplatin-based chemotherapy alone. In addition to being potentially more effective than adjuvant cisplatin-based chemotherapy in *EGFR* mutation-positive patients, EGFR TKIs have fewer side effects making them an appealing treatment option for patients with stage IA NSCLC, a subgroup for which no adjuvant therapy currently exists.[7]

An important example of molecularly targeted adjuvant therapy for patients with resected solid tumors is imatinib mesylate (Gleevec) therapy for patients with gastrointestinal stromal tumors, which express KIT protein (CD117) by immunohistochemistry.[26–29] A 770 patient randomized, placebo-controlled phase 3 trial demonstrated an improvement in DFS for the imatinib mesylate arm (hazard ratio: 0.35; 95% CI: 0.22–0.53, $p < 0.0001$).[28] To date, an improvement in OS from adjuvant imatinib has not been established. Studies are ongoing to determine whether the decision to treat, or dose of imatinib, should vary based on the presence of *KIT* gene mutations.

As for adjuvant use of EGFR TKI for patients with resected *EGFR* mutant lung adenocarcinoma, there are no randomized trials directing this therapy. A multicenter, single-arm, phase 2 trial (NCT00567359) is underway at Massachusetts General Hospital, Massachusetts General Hospital affiliated hospitals, and MSKCC, which will prospectively enroll 100 patients with resected NSCLC and activating mutations in *EGFR* to receive erlotinib 150 mg daily dose for up to 2 years after completion of all standard adjuvant chemotherapy and radiation therapy.[30] Thirty-six patients have been enrolled during a course of 2 years. Rash, fatigue, and diarrhea were the most common grade 3 toxicities occurring in 14, 3, and 6% of patients, respectively. Ten (28%) patients were dose reduced to erlotinib 100 mg ($n = 6$) and 50 mg ($n = 4$) due to toxicities, and five (14%) have withdrawn as a result of toxicity or patient preference.[30] The primary end point is DFS at 2 years. Because this is a single-arm trial, the data for patients with resected stages I to III NSCLC and *EGFR* mutation who do not receive EGFR TKI being collected at MSKCC will serve as an important historical comparator.

Two randomized trials of adjuvant EGFR TKI for patients with resected NSCLC have been initiated, but neither trial is enriched for patients with *EGFR* mutations. There is consensus that the greatest benefit of EGFR TKI therapy occurs in metastatic patients with *EGFR* mutations[12] and that there is growing concern that there may be harm to *EGFR* wild type or *KRAS* mutant patients treated with erlotinib or gefitinib.[12] Any data from EGFR TKI trials that do not select patients based on presence of *EGFR* mutations may be misleading.

The phase 3 National Cancer Institute of Canada BR19 trial comparing adjuvant gefitinib versus placebo in patients with completely resected NSCLC was initiated but closed early for safety concerns after interim analysis of phase 3 S0023 trial showed that maintenance gefitinib was worse than placebo in unselected patients with inoperable stage III NSCLC.[31] As a result, BR19 accrued 503 of planned 1160 patients with median duration of active study therapy for less than 5 months. The study eligibility criteria did not mandate

TABLE 4. Multivariate Overall Survival Analysis

n = 167	*N* (Event *N*)	2-yr Survival (95% CI)	Adjusted Hazard Ratio[a] (95% CI)	Adjusted *p*
Adjuvant erlotinib/gefitinib	56 (8)	96% (85–99)	0.62 (0.26–1.51)	0.296
No adjuvant erlotinib/gefitinib	111 (21)	90% (82–95)		

[a] Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.
CI, confidence interval.

selection of patients based on molecular or clinical characteristics that correlate with sensitivity to gefitinib such as adenocarcinoma histology, female gender, never smoking status, or East Asian ethnicity.[32,33] The majority of patients enrolled in BR19 were former or current smokers and included patients with squamous cell histology.[34] Tissue samples from 357 of 503 patients who received treatment on BR19 were studied with the goal of demonstrating a clinical benefit for adjuvant gefitinib in the subgroup of patients with *EGFR* mutations. Mutation status in 30% of patients treated on BR19 remains unknown. Because the BR19 patient population was not enriched for presence of *EGFR* mutations and mutation testing was limited to a subgroup of patients, only 76 patients with *EGFR* mutations (40 in the placebo arm and 36 in the gefitinib arm) were included in the study.[34] The incidence for grade 3 or 4 adverse events was very low, with dyspnea being the most common serious adverse event and equally balanced between gefitinib and placebo arms seen in 5% of patients in each treatment arm. A higher incidence of pneumonitis was noted in the placebo arm. In an exploratory analysis in a subset of patients with *EGFR* mutations, gefitinib therapy did not result in disease free or OS benefit.[34] Taking into account that this was a subgroup analysis of an underpowered study that was terminated early with some patients receiving only a few days of study therapy, the results of BR19 cannot be used to draw conclusions about the impact of adjuvant EGFR TKIs in patients with lung adenocarcinoma and *EGFR* mutation.

The Randomized Double-Blind Trial In Adjuvant NSCLC with Tarceva (RADIANT) is another phase 3 trial that is currently investigating adjuvant erlotinib therapy in patients with resected NSCLC who have overexpression of EGFR protein by immunohistochemistry or *EGFR* gene amplification by fluorescence in situ hybridization. Although *EGFR* mutations are not a prerequisite for the RADIANT study entry, *EGFR* mutation analysis was performed on tumors from 278 patients enrolled to date. As expected, the rate of EGFR exon 19 and 21 mutations in this unselected patient population is 12%.[35] The planned accrual for the RADIANT trial is 945 patients, which will result in approximately 113 patients (approximately 60 patients per treatment arm) with tumors that harbor *EGFR* mutation. Again, based on our data, it is unlikely that a significant difference in outcomes can be demonstrated in this number of patients. Subdividing the data into subgroups reduces the study's power to detect treatment differences by reducing the sample size and increasing the number of statistical tests needed to test for an interaction between different clinical factors.[36]

In contrast to the RADIANT and BR19 trials, our cohort consists exclusively of patients with resected lung adenocarcinomas with *EGFR* mutations. The majority of molecular testing on our patients was performed prospectively, and all testing was done at a single laboratory. In regard to surgery and chemotherapy, the majority of the patients in this cohort had uniform management for their lung adenocarcinoma by the MSKCC Thoracic Disease Management Team.

Although the large number of patients from a single institution makes this data important, there are limitations to our analysis. Treatment with adjuvant erlotinib/gefitinib was largely dependent on the patients' and their oncologists' preference. Seventy percent of patients who received the EGFR TKI had stages I and II disease, and given the long natural history of early stage *EGFR* mutant lung adenocarcinoma, the 2-year DFS may be too short to adequately reflect the population outcome. Patients with more advanced tumors were more likely to be offered, or motivated, to take adjuvant TKI therapy as an innovative therapy after surgery and completion of standard adjuvant therapy. Because more high-risk patients were treated with adjuvant TKI, this would tend to bias the results against the therapeutic impact of the TKI. We accounted for differences in prognostic variables between patients who did and did not receive adjuvant TKI by adjusting for age, sex, and pathologic stage through a multivariate analysis. A proportion of patients received gefitinib therapy preoperative and postoperatively, whereas others only received erlotinib postoperatively. Finally, we did not control for the doses or duration of EGFR TKI therapy, and we did not collect toxicity data prospectively, although no patient was identified whose death was attributed to treatment with erlotinib or gefitinib.

Despite the study limitations, we have demonstrated for the first time that adjuvant therapy with erlotinib or gefitinib in patients with resected lung adenocarcinoma harboring *EGFR* mutations may have an impact on DFS (hazard ratio 0.53, 95% CI: 0.28–1.03, $p = 0.06$). Given the potential magnitude of DFS benefit our data support, and the relatively small number of patients needed in a randomized trial to confirm these observations, a phase 3 trial is justified. The primary end point should be DFS, the same end point that was used in the trial that lead to the approval of imatinib in patients with KIT-positive gastrointestinal stromal tumors.[26,27] OS cannot be used as the primary end point because virtually all patients with recurrent lung adenocarcinoma and *EGFR* mutation will receive an EGFR TKI at recurrence. Based on our results, the number of *EGFR* mutation-positive lung adenocarcinoma cases in RADIANT (estimate $n = 120$), BR19 ($n = 76$), and the ongoing single-arm NCT00567359 trial ($n = 100$) pooled together will be insufficient to prove a clinically significant DFS advantage of adjuvant EGFR TKI therapy. Appropriate patient selection with deliberate trial design and sample size justification will be essential to demonstrate the survival benefit for adjuvant therapy in a resected lung adenocarcinoma population that may have a favorable prognosis irrespective of therapy.

This analysis was performed to provide the framework for further investigation of adjuvant EGFR TKI therapy in patients with lung adenocarcinoma with *EGFR* mutations. On the basis of this data, we propose a phase 3 study to detect a 47% reduction in the risk of lung cancer recurrence or death. To demonstrate this improvement in DFS, 320 patients would be needed, with 160 patients per treatment arm, during a 3-year accrual time, and 2-year follow-up (trial design proposed in Figure 2). This design provides 85% power at 5% type I error rate. There is a theoretical possibility that adju-

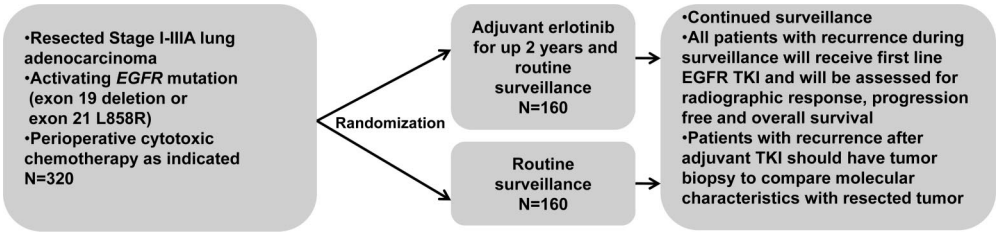

FIGURE 2. Schema for a clinical trial of adjuvant erlotinib or gefitinib. Primary end point is disease-free survival proportion at 2 years from time of randomization. EGFR, epidermal growth factor receptor.

vant TKI might improve DFS, but injure patients or breed-resistant clones, which, in the long run, might result in worse OS. As such, we propose that the validation protocol will measure OS and mandate that enrolled patients with recurrent cancer must be treated with first-line TKI at recurrence, thus allowing a comparison of radiologic response rate and progression-free survival between the two arms of the study at recurrence giving early insight into the potential problem of acquired resistance to EGFR TKIs, which may develop from adjuvant TKI therapy.

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