Distinct Clinical Course of *EGFR*-Mutant Resected Lung Cancers

Results of Testing of 1118 Surgical Specimens and Effects of Adjuvant Gefitinib and Erlotinib

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Background: *EGFR* and *KRAS* mutations are mutually exclusive and predict outcomes with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment in patients with stage IV lung cancers. The clinical significance of these mutations in patients with resected stage I–III lung cancers is unclear.

Methods: At our institution, resection specimens from patients with stage I–III lung adenocarcinomas are tested for the presence of *EGFR* or *KRAS* mutations during routine pathology analysis such that the results are available before consideration of adjuvant therapy. In a cohort of 1118 patients tested over 8 years, overall survival was analyzed using multivariate analysis to control for potential confounders, including age, sex, stage, and smoking history. The impact of adjuvant erlotinib or gefitinib was examined in an independent data set of patients exclusively with *EGFR* mutation, in which date of recurrence was recorded.

Results: In the overall population, we identified 227 *KRAS* (25%) and 222 *EGFR* (20%) mutations. Patients with *EGFR*-mutant lung cancers had a lower risk of death compared with those without *EGFR* mutations, overall survival (OS) HR 0.51 (95% confidence interval [CI]: 0.34–0.76, $p < 0.001$). Patients with *KRAS*-mutant lung cancers had similar outcomes compared with individuals with *KRAS* wild-type tumors, OS HR 1.17 (95% CI: 0.87–1.57, $p = 0.30$). A separate data set includes only patients with *EGFR*-mutant lung cancers identified over 10 years ($n = 286$). In patients with resected lung cancers and *EGFR* mutation, treatment with adjuvant erlotinib or gefitinib was associated with a lower risk of recurrence or death, disease-free survival HR 0.43 (95% CI: 0.26–0.72, $p = 0.001$), and a trend toward improved OS.

Conclusions: Patients with resected stage I–III lung cancers and *EGFR* mutation have a lower risk of death compared with patients without *EGFR* mutation. This may be because of treatment with EGFR TKIs. Patients with, and without *KRAS* mutation have similar OS. These data support reflex testing of resected lung adenocarcinomas for *EGFR* mutation to provide prognostic information and identify patients for enrollment on prospective clinical trials of adjuvant EGFR TKIs.

Key Words: EGFR, KRAS, Early-stage, Resected, Lung cancers, Non–small cell lung cancers, Adenocarcinomas.

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Complete surgical resection is the best way to cure patients with early-stage (I–III) non–small cell lung cancers (NSCLCs). Pathologic stage is the most important prognostic factor for these patients, with 5-year survival proportions of 73% for pathologic stage IA, 58% for pIB, 46% for pIIA, 36% for pIIB, 24% for pIIIA, and 9% for pIIIB.[1] Patients with resectable stage II–III disease, who are treated with perioperative cisplatin-based chemotherapy have a lower risk of death (approximate 20% relative risk reduction) compared with patients treated with surgery alone.[2,3] Favorable prognostic factors include female sex, younger age, better performance status, lobectomy (as opposed to pneumonectomy or lesser resection), and squamous histology (for stages IB–II).[4–7]

Patients with stage IV NSCLCs and *EGFR* mutation have a better prognosis than patients without *EGFR* mutation, and are more likely to benefit from treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).[8–11] In patients with stage IV NSCLCs, *KRAS* mutations are not prognostic, and predict a lack of benefit from EGFR TKIs.[12,13] In patients with surgically resected stage I–III lung cancers, data on the prognostic or predictive value of *EGFR* or *KRAS* mutations are limited.[14–17]

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Patients at Memorial Sloan-Kettering Cancer Center (MSKCC) with resected stage I–III lung adenocarcinomas have their tumor tested for *EGFR* and *KRAS* mutations as part of routine care, with results available to the medical oncologist during consideration of adjuvant therapy.[18] The prognostic value of *EGFR* and *KRAS* mutations in patients with lung adenocarcinomas has been assessed by our group in the past, with results published in the *Journal of Thoracic Oncology* in 2008.[19] This initial study included 296 total patients, of which 14% and 17% of patients were found to have *EGFR* and *KRAS* mutations in their tumor tissue, respectively. Patients who had ever received treatment with an EGFR TKI (gefitinib or erlotinib) were excluded from this initial study. After adjusting for stage, *EGFR*-mutant patients had a trend toward improved survival compared with those who were *EGFR/KRAS* wild-type, which did not reach statistical significance (HR 0.4, [95% CI: 0.1–1.4]).[19] Also in the *Journal of Thoracic Oncology*, our group has reported the impact of adjuvant EGFR TKI therapy on 167 patients with resected *EGFR*-mutant lung cancers in which date of disease recurrence was recorded to allow for analysis of disease-free survival.[20] In this independent study, treatment with adjuvant erlotinib or gefitinib was associated with a trend toward improved disease-free and overall survival (OS) that did not reach statistical significance.[20]

This current study represents an update of both prior studies from our institution. The data sets for each study have been maintained and updated independently, but are reported here together, given their relevance.

MATERIALS AND METHODS

We analyzed tumor specimens from patients with surgically resected adenocarcinomas of the lung seen at MSKCC from January 2002 to December 2009, using an Institutional Review Board approved tissue procurement protocol. After microscopic examination confirmed the diagnosis of adenocarcinoma, tissue was sent to a molecular diagnostic laboratory in the Department of Pathology for extraction of DNA and identification of *EGFR* exon 19 deletions and exon 21 L858R mutations by nonsequencing based polymerase chain reaction assays.[21] In samples lacking these two sensitizing *EGFR* mutations, *KRAS* analysis was done by direct sequencing of exon 2 using polymerase chain reaction products.

Patients were excluded if they were found to have stage IV disease at the time of surgery or had incomplete resections. Compared with our prior study,[19] this updated study included many more patients who had received treatment with EGFR TKIs, both in the adjuvant setting, and at recurrence. A high risk of recurrence (i.e., higher stage), and actual recurrence, increased the likelihood of treatment with an EGFR TKI. As such, it was no longer reasonable to exclude patients who had received EGFR TKIs from the analysis. Therefore, in contrast to the prior study, all patients who received an EGFR TKI at any time in their treatment course were included in the analysis.

Pathologic stage was updated according to the *American Joint Committee on Cancer* guidelines, 7th edition.[22] Smoking status was characterized as follows: never smokers (<100 lifetime cigarettes), former smokers (quit more than 1 year before diagnosis), or current smokers (quit less than 1 year before diagnosis). OS was determined using institutional databases and the Social Security Death Index. Clinical characteristics were compared among the three groups determined by mutation status (*EGFR*-mutant, *KRAS*-mutant, no mutation in *EGFR* or *KRAS)* using Fisher's exact test. For OS, patients were followed from the date of surgery until death. Patients who were alive were censored at the time of the last available follow-up. OS was estimated using the Kaplan–Meier method, with follow-up starting at the time of surgical resection. Survival comparisons among groups were performed using the log-rank test adjusted for pathological stage.[23] A multivariate Cox proportional hazards model was fit to investigate the effect of mutation on OS, adjusted for age, sex, smoking status, and stratified by pathological stage. The effect of perioperative platinum-based chemotherapy was examined in all patients and separately for each pathological stage using Cox proportional hazard models adjusted for the same factors. Receipt of chemotherapy was treated as a time-dependent variable.

We also performed an update of our database made up exclusively of patients with completely resected stage I–III lung cancer and *EGFR* mutation identified by reflex testing.[20] This update included patients who had surgery through October 2010 and therefore includes more patients identified to have *EGFR* mutation than the prior data set did, which included all resected patients from 2002 to 2009. This database also included detailed information regarding date of disease recurrence, allowing for analysis of both OS, and disease-free survival (DFS). For this update, follow-up was extended through July 2011. DFS was defined as time from surgical resection to cancer recurrence or death from any cause. DFS and OS were compared between patients with *EGFR*-mutant lung cancers who did, and did not receive an adjuvant EGFR TKI using multivariate Cox regression analyses.

In this data set, only dates of adjuvant erlotinib or gefitinib delivery were recorded. Patients at MSKCC receive adjuvant erlotinib or gefitinib by enrolling in phase 2 clinical trials,[24,25] or outside of a clinical trial. In all cases, adjuvant erlotinib or gefitinib is prescribed at the Food and Drug Administration approved dose for stage IV disease, with the goal to deliver daily oral therapy for up to 2 years. Whether on or off a research protocol, therapy is initiated after completion of all standard adjuvant chemotherapy (typically 4 cycles of cisplatin-based chemotherapy). Patients with resected IIIA(N2) disease also complete postoperative radiation therapy before starting adjuvant EGFR TKI. In addition to up to 2 years of postoperative therapy, a minority of patients also received gefitinib or erlotinib before surgery, for 21 days on protocol,[24] or up to 3 months off protocol. Reasons for stopping postoperative erlotinib or gefitinib include disease recurrence, intolerable side effects, completion of 2 years of adjuvant therapy, or physician or patient preference. A minority of patients continued to take postoperative erlotinib or gefitinib beyond 2 years based on physician or patient preference.

In the survival analysis, adjuvant 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 EGFR TKI. All significance tests

were two-sided and used a 5% level of significance. Statistical analyses were performed using SAS (SAS Institute, Inc., Cary, NC) software and packages "clinfun" and "survcomp" in R (http://www.r-project.org/).

RESULTS

Demographics of 1118 patients with resected lung adenocarcinoma tested for *EGFR* and *KRAS* mutations are presented in Table 1. We detected *KRAS* mutations in 277 specimens (25%; 95% CI: 22%–27%) and *EGFR* mutations in 222 specimens (20%; 95% CI: 18%–22%). More patients with *EGFR*-mutant lung cancers were never smokers (60%) compared with *KRAS* (4%), p value was less than 0.001. Among individuals with *EGFR*-mutant lung cancers, 53 (24%) received adjuvant TKI, 19 (9%) received TKI only at recurrence, and 11 (5%) received it both in the adjuvant setting and at recurrence.

Patients had a median follow-up of 27 months (range, 0.3–107 months). Median survival for all 1118 patients was 77 months. Lower tumor stage and female sex were good prognostic factors (Table 2). Never smoking was also a statistically significant good prognostic factor.[26] At 3 years, OS proportion among current smokers was 62% (95% CI: 53%–73%), former smokers 77% (95% CI: 74%–81%), and never smokers 80% (95% CI: 75%–86%), p value was 0.03. There was no effect of age on the risk of death up to 65 years. After that, the risk of death increased linearly with age, with hazard ratio 1.05 (95% CI: 1.02–1.09, $p = 0.005$).

After adjusting for pathologic stage, the median OS was better for patients with *EGFR*-mutant lung cancers (83 months, 95% CI: 76 months to not reached) compared with those with *KRAS*-mutant lung cancers (73 months, 95% CI: 62 months to not reached), p value was 0.003. Three-year OS was 87% for individuals with *EGFR*-mutant tumors (95% CI: 81%–92%) and 75% with *KRAS*-mutant disease (95% CI: 69%–82%). In a multivariate analysis, the presence of an *EGFR* mutation predicted improved survival compared to a *KRAS* mutation, HR 0.48 (95% CI: 0.30–0.77, $p = 0.002$).

Patients with *EGFR*-mutant lung cancers had improved survival compared with patients who did not have *EGFR*-mutant disease, adjusted HR 0.51 (95% CI: 0.34–0.76, $p < 0.001$) (Fig. 1**).** In contrast, there was no difference in the survival of patients with tumors with and without a *KRAS* mutation detected in their resection specimen, adjusted HR 1.17 (95%CI: 0.87–1.57, $p = 0.30$) (Fig. 2).

A separate database includes only patients with resected lung adenocarcinoma and *EGFR* mutation identified at the time of surgery. Demographics of 286 patients with resected lung adenocarcinoma and *EGFR* mutation are presented in Table 3. Patients underwent surgery through July 2011, and median follow-up was 34 months (95% CI: 30–37, range, 1–108 months). Eighty-four of 286 patients (29%) received adjuvant gefitinib or erlotinib. Median duration of adjuvant EGFR TKI was 18.6 months (range, 0.1–51.4 months).

Using a Cox regression analysis, patients with *EGFR*-mutant lung cancers who received adjuvant gefitinib or erlotinib demonstrated a longer disease-free survival than those who did not receive an adjuvant EGFR TKI, HR 0.43 (95%CI: 0.26–0.72, $p = 0.001$) (Fig. 3). Patients who received adjuvant gefitinib or erlotinib showed a numerically superior OS, however, this difference was not significant, HR 0.50 (95% CI: 0.23–1.08, $p = 0.076$) (Fig. 4). This observation of improved outcome in patients with resected NSCLCs and *EGFR* mutation treated with adjuvant EGFR TKI is despite the fact that patients who received adjuvant EGFR TKI tended to have a

TABLE 1. Clinical Characteristics of 1118 Patients with Resected Stage I–III Lung Adenocarcinoma Tested for EGFR and KRAS Mutation

	***EGFR* Mutation** ***n* = 222** **(20% of total)**	***KRAS* Mutation** ***n* = 277** **(25% of total)**	**No *EGFR* or *KRAS* Mutation Detected** ***n* = 619** **(55% of total)**
Median age, yrs (range)	68 (35–89)	68 (39–86)	68 (23–96)
Stage			
IA	120 (54%)	150 (54%)	318 (51%)
IB	42 (19%)	39 (14%)	126 (20%)
IIA	15 (7%)	25 (9%)	46 (7%)
IIB	16 (7%)	20 (7%)	34 (6%)
IIIA	27 (12%)	37 (14%)	72 (12%)
IIIB	2 (1%)	6 (2%)	23 (4%)
Tumor size (cm)			
<2	106 (48%)	135 (49%)	299 (48%)
2–3	68 (31%)	69 (25%)	158 (26%)
3–5	45 (20%)	50 (18%)	116 (19%)
5–7	2 (<1%)	10 (4%)	25 (4%)
>7	1 (<1%)	10 (4%)	10 (2%)
Cigarette smoking			
Never	134 (60%)	12 (4%)	92 (15%)
Former	84 (38%)	213 (77%)	435 (70%)
Current	4 (2%)	52 (19%)	92 (15%)
Cytotoxic chemotherapy			
None	176 (80%)	214 (77%)	440 (71%)
Adjuvant/neoadjuvant	46 (21%)	63 (23%)	179 (29%)

TABLE 2. Overall Survival Analysis for 1118 Patients with Resected Stage I–III Lung Adenocarcinoma Tested for EGFR and KRAS Mutation

Variable	Category	N	3-Yr Overall Survival (95% CI)	*p* (Adjusted for Stage)
Stage				
	IA	588	88% (84%–91%)	Ref
	IB	207	75% (68%-–82%)	0.002
	II	156	62% (54%–72%)	<0.001
	III	167	53% (45%–62%)	<0.001
Sex				
	F	710	80% (76%–84%)	Ref
	M	408	70% (64%–75%)	0.001
Mutation type				
	EGFR mutation	222	87% (81%–92%)	Ref
	KRAS mutation	277	75% (69%–82%)	0.003
Smoking history				
	Never	238	80% (75%–86%)	Ref
	Former	732	77% (74%–81%)	0.053
	Current	148	62% (53%–73%)	0.007

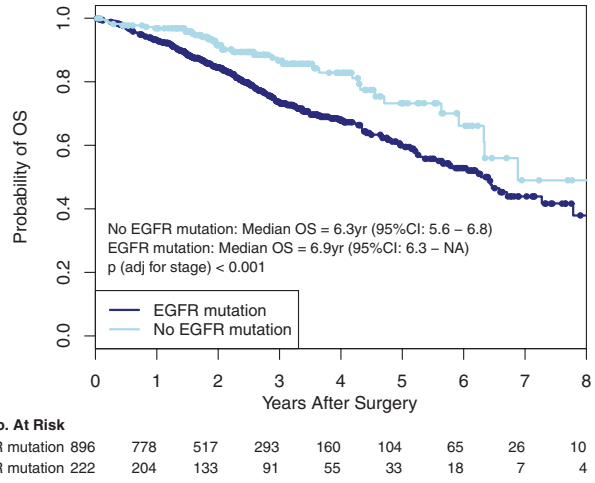

FIGURE 1. OS comparing patients with *EGFR*-mutant versus *EGFR* wild-type tumors. OS, overall survival; CI, confidence interval; NA, not available.

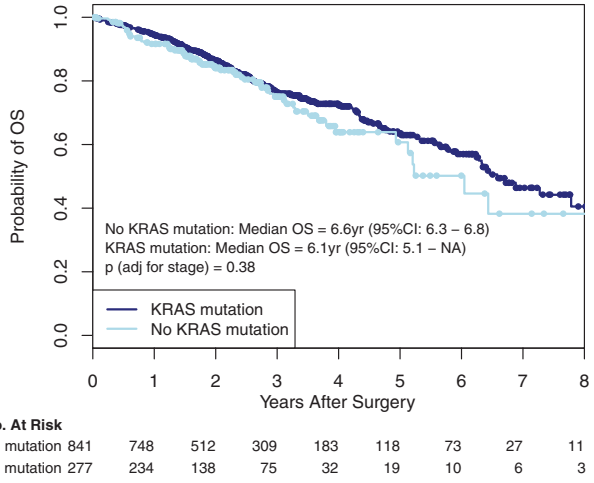

FIGURE 2. OS comparing patients with *KRAS*-mutant versus *KRAS* wild-type tumors. OS, overall survival, CI, confidence interval; NA, not available.

higher stage of disease (48% stage II–III), compared with patients who did not receive adjuvant EGFR TKI (16% stage II–III), *p* value was less than 0.001. Because patients who received adjuvant EGFR TKI tended to have a higher stage of disease, they were also more likely to have also received cytotoxic chemotherapy before starting adjuvant EGFR TKI (45% versus 16%, $p < 0.001$).

DISCUSSION

Despite successful surgery, half the patients with resected lung cancers suffer recurrence and death within 5 years.[27] Pathologic stage is the most important factor for selecting patients for adjuvant cisplatin-based chemotherapy, the only additional treatment known to improve the likelihood of cure. Other than stage, there are no validated clinical factors that predict the benefit of adjuvant treatment. Better prognostic and predictive biomarkers are needed to identify which patients should be treated with adjuvant therapy, and which agents to use.

In this analysis of 1118 patients with resected lung adenocarcinomas, we evaluated the prognostic significance of *EGFR* and *KRAS* mutations, conscious of the rising use of EGFR TKIs at recurrence and our institutional interest in studying adjuvant EGFR TKIs for patients with *EGFR*-mutant lung cancers.[24,28] We limited *EGFR* mutation testing to the most common *EGFR* mutations, exon 19 deletions and exon 21 L858R, which represent more than 90% of activating mutations that impart erlotinib and gefitinib sensitivity. We limited *KRAS* mutation testing to the most common *KRAS* mutations found in exon 2. Using these methods, and adjusting for potential confounders, we observed a lower risk of death in patients with *EGFR*-mutant lung cancers compared with all patients whose tumors did not harbor *EGFR* mutations, and compared with those with *KRAS*-mutant lung cancers. In

TABLE 3. Clinical Characteristics of 286 Patients with Resected Stage I–III Lung Adenocarcinoma and EGFR Mutation Comparing Patients Who Did or Did Not Receive Treatment with Adjuvant EGFR TKI

	Received Adjuvant EGFR TKI (n = 84)	No adjuvant EGFR TKI (n = 202)	p
Age, yrs: median (range)	65 (36–88)	70 (35–90)	0.002*
Sex—no. (%)			
Male	22 (26%)	54 (27%)	1.000
Female	62 (74%)	148 (73%)	
Pathologic stage—no. (%)			
I	44 (52%)	169 (84%)	<0.001
II	14 (17%)	17 (8%)	
III	26 (31%)	16 (8%)	
Neoadjuvant/adjuvant cytotoxic chemotherapy—no. (%)			
Yes	38 (45%)	32 (16%)	<0.001
No	46 (55%)	170 (84%)	

*p value calculated using Wilcoxon rank-sum test. Other p values calculated using Fisher's exact test.
EGFR, ; TKI, tyrosine kinase inhibitor.

contrast, detection of a *KRAS* mutation did not affect OS compared with all patients without a *KRAS*-mutant tumor.

To our knowledge, this is the largest series evaluating the impact of *EGFR* mutations on survival in resected NSCLCs. The prognostic and predictive values of *KRAS* mutations have been studied in a series of 1500 patients with resected NSCLCs collected from trials in which patients were randomly assigned to surgery alone or surgery followed by adjuvant cisplatin-based chemotherapy (LACE-Bio).[29] There were 303 patients (20%) in whom *KRAS* mutations were detected in their resection specimens. There was no difference in OS comparing patients with *KRAS*-mutant lung cancers with those with *KRAS* wild-type tumors (HR 1.18, $p = 0.09$).[29] No significant benefit of adjuvant chemotherapy was observed in patients with *KRAS*-mutant tumors (HR 1.02, 95% CI: 0.73–1.41, $p = 0.91$), or in individuals with *KRAS* wild-type tumors (HR 0.89, 95% CI: 0.76–1.06, $p = 0.20$). There was no significant interaction to suggest that the presence of a *KRAS* mutation should be used as a predictive marker to select adjuvant cisplatin-based chemotherapy. Our results confirm the lack of prognostic implications of *KRAS* mutation in resected lung cancer.

Recently, the prognostic roles of *EGFR* and *KRAS* mutations were evaluated in 164 Taiwanese patients with resected disease.[16] In that analysis, the median survival was numerically longer for patients with *EGFR*-mutant lung cancers (55

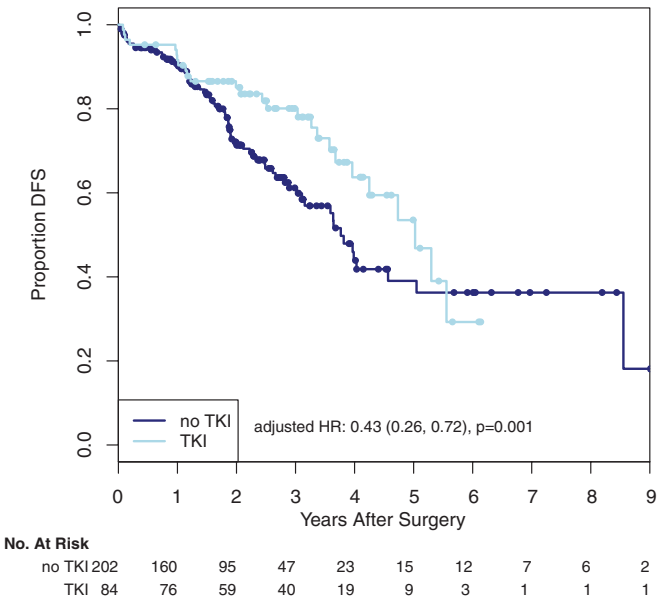

FIGURE 3. DFS in patients with *EGFR*-mutant lung cancer with (TKI) and without (no TKI) adjuvant gefitinib or erlotinib. DFS, disease-free survival; TKI, tyrosine kinase inhibitors; HR, hazard ratio.

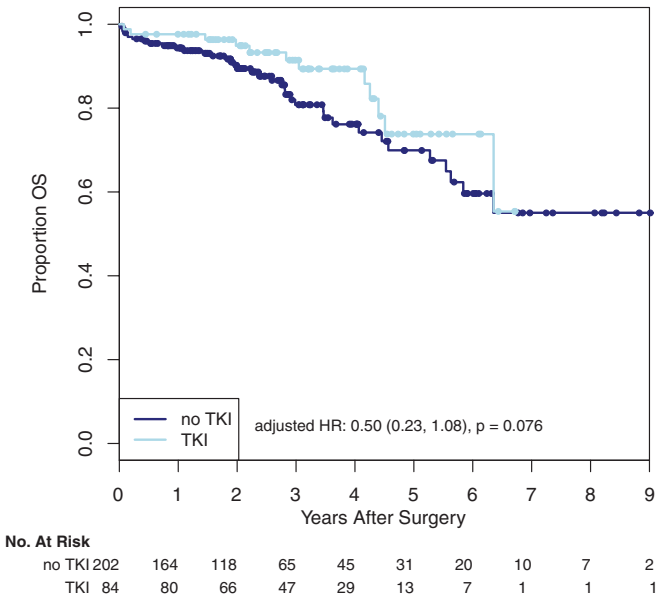

FIGURE 4. OS in patients with *EGFR*-mutant lung cancer with (TKI) and without (no TKI) adjuvant gefitinib or erlotinib. OS, overall survival, TKI, tyrosine kinase inhibitors; HR, hazard ratio.

months) than in individuals with *EGFR* and *KRAS* wild-type tumors (35 months). However, this difference was not significant ($p = 0.2$). The 3-year survival for patients with *EGFR*-mutant lung cancers was significantly better than the survival observed in those with tumors wild-type for *EGFR* and *KRAS* ($p = 0.02$). These differences did not change when the patients who received an EGFR TKI were removed from the analysis. In a larger study of Japanese patients, the superior survival of the patients with *EGFR*-mutant tumors compared with those with *KRAS* or *TP53* gene mutations was no longer significant after multivariate analyses, although any patient who received an EGFR TKI was excluded from the survival analysis.[15]

The lower risk of death in patients with resected lung adenocarcinomas with *EGFR* mutations may be because of disease biology (*EGFR* mutation as a prognostic factor), or the effect of treatment with an EGFR TKI (*EGFR* mutation as a predictive factor). It is difficult to distinguish the prognostic from the predictive impact of an *EGFR* mutation in a retrospective study in which the patients who received an adjuvant EGFR TKI tended to have higher-stage disease, and patients who received any EGFR TKI tended to have recurrent disease. This bias toward treating patients with *EGFR* mutation and a higher risk of death with an adjuvant EGFR TKI in a retrospective study could underestimate the value of an EGFR TKI in reducing the risk of death.

In our study of patients with resected stage I-III NSCLC and *EGFR* mutation detected by reflex testing, we compared outcomes in patients who did, and did not receive treatment with adjuvant EGFR TKI. This study combined patients who had been treated with adjuvant EGFR TKI (either gefitinib or erlotinib) on two clinical trials at MSKCC, and also off protocol, for a total of 84 patients treated with adjuvant EGFR TKI. A prospective, placebo-controlled study (NCT00373425; RAndomized Double-blind trial In Adjuvant NSCLC with Tarceva, RADIANT) of adjuvant erlotinib in patients with resected NSCLC did not enrich exclusively for patients with *EGFR* mutation, and at close of enrollment was estimated to have included 113 patients with *EGFR* mutation, half of whom were randomized to placebo.[29] Results of the RADIANT study are pending, with DFS as the primary endpoint. A prospective, placebo-controlled study (NCIC BR19) of adjuvant gefitinib in patients with resected NSCLC also did not enrich for *EGFR* mutation, and only genotyped 357 of 503 patients enrolled. Of those genotyped, only 76 patients were found to have *EGFR* mutations (40 in the placebo arm and 36 in the gefitinib arm).[30]

For all patients at MSKCC, in the RADIANT and NCIC BR19 studies, the goal has been to deliver up to 2 years of adjuvant EGFR TKI therapy. In our study, the median duration of adjuvant EGFR TKI therapy was 18.6 months. When adjusted for stage, age, sex, and smoking history, there was a reduced risk of disease recurrence in patients who had *EGFR*-mutant lung cancers and received adjuvant EGFR TKI compared with patients who had *EGFR*-mutant lung cancer and did not receive an adjuvant TKI; DFS HR 0.43 (95% CI: 0.26–0.72, $p = 0.001$). In contrast to our previous data published in the *Journal of Thoracic Oncology* in early 2011, this result shows the same trend but is now statistically significant. The OS trend in this data set remains favorable, but is not statistically significant; HR 0.50 (95% CI: 0.23–1.08, $p = 0.076$).

Testing tumor tissue from patients with recurrent, or stage IV NSCLC for *EGFR* mutations is a standard of care.[31,32] Randomized phase III studies of patients with metastatic *EGFR*-mutant lung cancers have demonstrated improved progression-free survival and radiologic response rates with gefitinib or erlotinib compared with platinum-based chemotherapy.[8–11] In addition, patients with stage IV *EGFR*-mutant lung cancers have a higher response rate to platinum-based chemotherapy compared with patients with *EGFR* wild-type tumors.[10] Studies in patients with stage IV NSCLC also suggest that those with *EGFR*-mutant tumors have a better prognosis, with median survival times of 24 to 36 months compared with 12 months or less in those with *EGFR* wild-type tumors.[33] No study in stage IV patients has ever shown an improvement in OS with earlier treatment with EGFR TKI because of crossover to EGFR TKI in patients initially treated with chemotherapy; however, survival trends are consistently favorable with the earlier use of EGFR TKI.[8,9,11,33] On the basis of these results, it is no surprise that we observe improvements in DFS but not OS in our series of resected patients treated with adjuvant EGFR TKI.

At MSKCC, where patients with resected NSCLCs are prescribed adjuvant therapy with knowledge of *EGFR* mutation available, our team is cautious not to consider EGFR TKI as a substitute for standard adjuvant therapies. A question remains whether the presence of an *EGFR* mutation in patients with resected (stage I–III) NSCLCs could impact the effectiveness of standard adjuvant chemotherapy. A subgroup analysis from the National Cancer Institute of Canada JBR.10 study looked for *EGFR* mutations in 436 of 482 patients with resected stage IB–II NSCLCs randomized to surgery alone, or surgery followed by adjuvant cisplatin + vinorelbine.[34] *EGFR* mutations were identified in 43 patients (10%), of whom 27 had been randomized to surgery alone, and 16 to surgery followed by cisplatin + vinorelbine. The benefit of adjuvant cisplatin + vinorelbine on DFS was numerically higher in the *EGFR*- mutant subgroup (HR 0.44, 95% CI: 0.11–1.70, $p = 0.22$) than in the subgroup with *EGFR* wild-type tumors (HR 0.78, 95% CI: 0.58–1.06, $p = 0.12$); however, this result was not significant (interaction $p = 0.50$).[34]

In our retrospective study, patients with *EGFR* mutation who received adjuvant EGFR TKI tended to have a higher stage of disease, and were also more likely to have also received up to four cycles of cisplatin-based chemotherapy. This highlights physician preference to provide more adjuvant therapy for patients with a higher risk of recurrence and death. This bias may impact enrollment of high-risk patients into placebo-controlled studies of adjuvant EGFR TKI.

In summary, we report the largest cohort of patients with *EGFR*-mutant lung cancers with the longest follow-up after treatment with adjuvant erlotinib or gefitinib. Our data are provocative but have been generated by analyzing a large case series and not the results of a randomized clinical trial, and our conclusions constitute a lower level of evidence than would be provided by a randomized clinical trial. Our data carry the reassurance that adjuvant EGFR TKI will not increase the risk of death, and the side effects of these drugs are well known and

manageable. Also reassuring is our observation that patients treated with adjuvant EGFR TKI maintain sensitivity to EGFR TKI if they recur after stopping adjuvant therapy.[34]

We believe these data justify reflex testing of resection specimens from patients with NSCLCs for *EGFR* mutations because they predict a lower risk of death. These results also mandate a prospective, randomized trial of an adjuvant EGFR TKI in individuals with *EGFR*-mutant lung cancers to determine whether early treatment can prevent, or delay, recurrence and death. A 100-patient phase II study (NCT00567359)[35] of adjuvant erlotinib for patients with resected *EGFR*-mutant lung cancers has completed enrollment, and early results are promising.[36] An intergroup trial of adjuvant erlotinib for resected *EGFR*-mutant lung cancer sponsored by the National Cancer Institute, United States is planned.

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