TO THE EDITOR: Patients with lung cancer who respond to gefitinib have been reported to have somatic mutations consisting of deletions in exon 19 and the L858R mutation in exon 21 of the epidermal growth factor receptor (EGFR) gene.\(^1\) In addition, a second mutation (T790M) in exon 20 is also associated with acquired resistance to gefitinib in initially gefitinib-sensitive patients.\(^2,3\) We describe a patient with gefitinib-resistant lung adenocarcinoma harboring both T790M and L858R at diagnosis.

A 55-year-old woman who had never smoked presented with blurred vision and slurred speech. Magnetic resonance imaging of the brain disclosed a rim-enhanced mass in the left parietal–occipital area. Computed tomography of the chest showed a mass in the right upper lung with enlarged lymph nodes in the lower neck and mediastinum. Percutaneous transthoracic biopsy guided by ultrasonography revealed lung adenocarcinoma. Gefitinib was started at a dose of 250 mg per day. The patient also underwent whole-brain radiotherapy and stereotactic radiosurgery for control of the brain tumor. One month later, the size of the lung tumor was unchanged, but at nine weeks, chest radiography revealed progression of disease. Gefitinib was stopped, and treatment was changed to chemotherapy with gemcitabine and cisplatin.

Screening for mutations of the kinase domain (exons 18 through 21) of EGFR by direct sequencing of DNA isolated from a lung-tumor–biopsy specimen and blood lymphocytes identified a T-to-G mutation at nucleotide 2573 of exon 21, resulting in L858R (Fig. 1A). A C-to-T mutation was identified at nucleotide 2369 of exon 20, resulting in T790M (Fig. 1B). The mutations were detected in both sense and antisense sequences of two independent polymerase chain reactions and were confirmed by subcloning.

Lung cancers harboring the EGFR L858R mutation have been reported to be responsive to gefitinib.\(^1\) The studies of cells expressing L858R revealed increased gefitinib sensitivity in vitro.\(^4\) The
T790M mutation was shown to confer resistance to gefitinib after it was introduced into the sequence of the wild-type EGFR and L858R mutant EGFR in vitro.2,3 The T790M mutation results in steric hindrance of binding of gefitinib to the ATP-kinase-binding pocket. The T790M mutation may cause acquired resistance to gefitinib.2,3 Our patient had concomitant T790M and L858R EGFR mutations in the original lung-biopsy specimen and showed primary resistance to gefitinib — a finding implying that a mutation in the T790M kinase domain can occur during the natural evolution of lung cancer. T790M mutant gefitinib-resistant clones may preexist at levels below the threshold of detection5 in some patients with lung cancer at presentation and then may expand selectively under gefitinib treatment, leading to the failure of gefitinib therapy.

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Responsiveness to Cetuximab without Mutations in EGFR

TO THE EDITOR: A large amount of information suggests that mutations in the kinase domain of epidermal growth factor receptor (EGFR) are critical for the efficacy of EGFR kinase inhibitors.1-3 However, the effect of EGFR mutations on the response to cetuximab has not been directly investigated. Barber et al.4 reported the absence of EGFR mutations in colorectal cancers and speculated that EGFR mutations were not required for the response to cetuximab, since it was an efficacious agent against this type of tumor.5 We sequenced the kinase domain of EGFR (exons 18, 19, and 21) in tumor samples from 38 patients participating in a cetuximab-monotherapy study for recurrent non–small-cell lung cancer and tumor samples from 39 patients participating in a cetuximab-monotherapy study for refractory colorectal cancer. Mutations previously detected in non–small-cell lung cancer1-3 were identified in 3 of the 38 patients with non–small-cell lung cancer. Of 13 patients with non–small-cell lung cancer whose disease was stable, 2 carried a del1470-750, and of 21 patients with progressive disease, 1 had an L861Q mutation. No mutations were identified in other patients with non–small-cell lung cancer who had a partial response (one patient) or for whom response data were unavailable (three patients). No mutations were detected in the samples from the 39 patients with colorectal cancer, including those from 20 patients who had a partial response and 1 who had a complete response.

From these results, it appears that the presence of an EGFR mutation is not a major determining factor for a positive response to cetuximab. Absence of an EGFR mutation in the samples of colorectal cancer, including those from patients who had a response to cetuximab, supports the speculation by Barber et al.4 that EGFR mutations are not required for the efficacy of cetuximab in colorectal cancer. (Some of the samples were chosen for sequence analysis on the basis of the clinical response, and thus the numbers we mention in this letter do not reflect the response rates in the trials.) In addition, we sequenced 160 biopsy samples of previously untreated colorectal cancer (provided by Dr. Sina Dorudi, Royal London Hospital, London) from patients outside the cetuximab trial and could not identify any mutation in exons 18, 19, and 21. This further confirms the general absence of EGFR mutations in colorectal cancer. Our results suggest...