Erlo tinib Response in an NSCLC Patient with a Novel Compound G719D+L861R Mutation in EGFR

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CASE REPORT
A 62-year-old never smoker white woman was diagnosed with stage IV lung adenocarcinoma. Staging revealed a left lower lobe primary, an associated pleural effusion and multiple bony and hepatic metastases (Fig. 1). An interventional radiology-guided core biopsy of the primary lesion was performed, which demonstrated a well-differentiated adenocarcinoma that was TTF-1 and CK7 positive and CK20 negative by immunohistochemistry. Epidermal growth factor receptor (EGFR) mutation analysis was performed via the EGFR Rotor-Gene Q Instrument (RGQ) polymerase chain reaction assay (Qiagen, Manchester, United Kingdom) showing a G719X mutation (exon 18). The patient was started on erlotinib at 150 mg daily. Restaging positron emission tomography/computed tomography revealed decreased size and metabolic activity of the primary lesion and resolution of a hepatic metastasis (Fig. 2). Approximately 9 months after starting erlotinib, restaging positron emission tomography/computed tomography revealed disease progression with new left pleural thickening and worsening effusion. A left-sided video-assisted thoracoscopic surgery with biopsy and pleurodesis was performed for symptom management and further molecular diagnostics. Mutational analysis performed at the Colorado Molecular Correlates Laboratory at the University of Colorado Hospital using the ABIPrism SNaPshot multiplex polymerase chain reaction platform (Applied Biosystems, Forest City, CA) followed by direct sequencing duplicated her previously known G719X mutation, which was further clarified to be a c.2156G > A (p.G719D) mutation in addition to a c.2582T > G (p.L861R) point mutation in exon 21. Repeat molecular testing of the patient’s original diagnostic biopsy was performed at Colorado Molecular Correlates Laboratory, with both mutations (G719D and L861R) identified. The patient continued on erlotinib postprocedure in anticipation of enrollment in a clinical trial when she presented with progressive confusion, memory loss, and disease progression in the central nervous system, as determined by magnetic resonance imaging. The patient elected to forgo further therapy and enrolled in hospice, passing 11 months after initial diagnosis.

COMMENT
Missense mutations at position 719 in exon 18 of EGFR gene (G719A/S/V/D) have been previously described, occurring in approximately 3% of all known EGFR mutations and cause constitutive activation of EGFR.1–3 Mutations at position 861 (most commonly L861Q) have been described, occurring in approximately 2% of all EGFR-mutant patients.1 The specific mutations identified in this case are the least common of mutations at these two loci, and compound mutations with G719D and L861R have not been previously described. A recent retrospective analysis described objective response rates (ORR) of 53.3% on EGFR tyrosine kinase inhibitors with a median progression-free survival (PFS) of 8.1 months, and a median overall survival (OS) of 16.4 months in a G719X patient cohort. A patient cohort with L861Q EGFR mutated NSCLC demonstrated an ORR of 60%, PFS and OS of 6.0 and 15.2 months, respectively. Both cohorts

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FIGURE 1. Combined positron emission tomography/computed tomography images with thoracic imaging (A and B) demonstrating disease burden at initial staging (A) and initial response (B). Axial images of hepatic metastases (C and D) from initial staging (C) and initial response (D).
performed comparatively worse than the cohort harboring the more common deletion exon 19 and L858R mutations (ORR 74.1%; PFS 8.5 months; OS 19.6 months). Direct sequencing of exon 18 to 21 in 79 known EGFR-mutation–positive patients demonstrated a compound mutation rate of 14% with three response-evaluable patients harboring a G719X compound mutation and modest response to erlotinib with no partial response greater than 8 months and no OS greater than 12 months. These outcomes are consistent with our patient’s excellent but short-lived response.

REFERENCES