variants were identified. The results of anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) FISH testing were negative. In view of his history of human immunodeficiency virus/acquired immunodeficiency syndrome and poor performance status (Eastern Cooperative Oncology Group performance status of 2), he was at increased risk for morbidity from cytotoxic chemotherapy. He began taking first-line afatinib, 40 mg daily. After 6 weeks of therapy, clinically and radiographically evident rapid progression of disease in his left chest wall and lung metastases developed. His best response by the Response Evaluation Criteria in Solid Tumors, version 1.1, was progressive disease. Afatinib was held at the time of progression, and he was transitioned to hospice care. He died 4 months from the time treatment was discontinued.

Discussion

The *EGFR* variant reported here has not been previously reported in the Catalog of Somatic Mutations in Cancer database.[3] To our knowledge, the G721R mutation in exon 18 of the *EGFR* gene has not previously been reported. Unlike in the case of the common hotspot alterations in the *EGFR* gene, the evidence of clinical actionability of rarer *EGFR* variants have not been fully elucidated. The lack of response to *EGFR* TKI in our patient highlights the need for additional investigation of the molecular mechanisms underlying clinical response to *EGFR* TKIs. Further efforts to catalogue clinical experiences with uncommon *EGFR* variants are essential to understand the relevance of these low-frequency alterations in routine clinical practice.

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Cluster Circulating Tumor Cell Is Crucial in Surgically Resected Lung Cancer

To the Editor:

I have read with interest the article from Crosbie et al. revealing that circulating tumor cells (CTCs) in the blood of the tumor-draining pulmonary vein (PV) was an indicator of early recurrence.[1] They chose the PV because of the low sensitivity of the CellSearch Circulating Tumor Cell Kit for detecting CTCs (Janssen Diagnostics LLC, Raritan, NJ) in the circulating peripheral blood.

I found tumor cell dislodgement by surgical manipulation to the peripheral circulating blood using the CellSearch system, but the sensitivity was low.[2] As such, we examined isolated tumor cells, surrogates of CTCs extracted from the PV of the resected lung, revealing that detection of isolated tumor cells was an indicator of early recurrence. In particular, detection of cluster CTCs by using the CD45 negative depression gravity method (RosettSep [Stemcell Technologies, Vancouver, Canada]) indicated a poor prognosis.[3] Recently, we found CTC dislodgement by detecting CTCs in the peripheral circulating blood, and detecting cluster CTCs using a size selection method (ScreenCell Cyto, ScreenCell, Westford, MA) was an indicator of early recurrence.[4]

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In view of my observation that a cluster CTC is a crucial indicator of poor prognosis, I also recommend further study of tumorigenesis of clustered CTCs referring the observation revealing high potential of malignancy of cluster CTCs.[5]

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CD74-ROS1 Fusion in NSCLC Detected by Hybrid Capture–Based Tissue Genomic Profiling and ctDNA Assays

To the Editor:

Given the benefits of targeted therapy for a subset of patients with advanced NSCLC, an ongoing challenge is to identify sensitizing genomic alterations. Critical to such effort is the deployment of optimized, well-validated assays in the course of clinical care. Herein, we describe a patient with metastatic NSCLC with a *ROS1* fusion detected by tissue and blood hybrid capture–based assays but not by another circulating tumor DNA (ctDNA) assay.

A 41-year-old female never-smoker of Southeast-Asian descent presented to a community hospital with chest pain and dyspnea. Computed tomography demonstrated an irregular, cavitary, nodular density in the left lower lobe (LLL) measuring 2.0 cm in the greatest dimension. Antibiotics were started and the patient was lost to follow-up. She presented again 8 months later with worsening symptoms and a left pleural effusion; the results of bronchalveolar lavage were negative for malignancy. Three months later, imaging revealed new diffuse pleural thickening and nodularity, fluid collected in the left pleural cavity, significant LLL collapse, and mild mediastinal and hilar lymphadenopathy, with a 6.8 × 5.8-cm liver mass invading the hemidiaphragm and axial bone lesions. Repeat positron emission tomography–computed tomography 2 weeks later showed complete collapse of the LLL and partial encasement of the left upper lobe bronchi with extensive metastatic disease involving the left pleura and diffuse lymphadenopathy.

Cytologic biopsy demonstrated a thyroid transcription factor 1–positive, napsin-positive, cytokeratin 7–positive but calretinin-negative adenocarcinoma consistent with pulmonary origin. The results of a Clinical Laboratory

Table 1. Genes Altered: Results of Molecular Diagnostic Assays

Other	Well-Validated Platforms	
First ctDNA assay	Tumor genomic profiling	Second ctDNA assay
Not identified	*CD74-ROS1*	*CD74-ROS1*
Not identified	*TP53* splice site *CDKN2A* mutation	*TP53* splice site
N/C	*RICTOR* amplification	N/C
N/C	*FGF10* amplification	N/C
N/C	*GATA6* amplification	N/C
N/C	*NKX2-1* amplification	N/C

ctDNA, circulating tumor DNA; *CD74*, CD74 gene; *TP53*, tumor protein p53 gene; *CDKN2A*, cyclin-dependent kinase inhibitor 2A gene; *RICTOR*, PRTOR independent companion of MTOR complex 2 gene; N/C, not captured; *FGF10*, fibroblast growth factor 10 gene; *GATA6*, GATA binding protein 6 gene; *NKX2-1*, NK2 homeobox 1 gene.

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