CASE REPORT

Acquired *EGFR* Mutation as the Potential Resistance Driver to Crizotinib in a *MET*-Mutated Tumor

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One major advance of the past decade in anticancer treatment is the advent of precision medicine and personalized therapy, which has led to several therapeutic successes.[1,2] The efficacy of targeted therapies is unavoidably limited in time, however, and acquired resistance ultimately occurs.

Here, we report the case of a 59-year-old white woman with no smoking history who was diagnosed with metastatic adenocarcinoma of the lung. At diagnosis, restricted molecular analysis of the primary tumor showed epidermal growth factor receptor (*EGFR*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), and Kristen rat sarcoma viral oncogene homolog (*KRAS*) wild type and the absence of anaplastic lymphoma kinase (*ALK*) translocation. After three lines of conventional therapy, she was included in a phase 1 trial evaluating a gamma secretase inhibitor, during which the disease remained stable for 18 months. A second lung biopsy sample (containing 40% tumor cells) was then obtained as part of the MOSCATO (Molecular Screening for Cancer Treatment Optimization) trial at Gustave Roussy Cancer Campus (NCT01566019). Comparative genomic hybridization analyses revealed an MDM2 proto-oncogene, E3 ubiquitin protein ligase (*MDM2*) amplification, and targeted next-generation sequencing showed a MET proto-oncogene, receptor tyrosine kinase (*MET*) activating mutation (NM_001127500.1:c.3082G>C; p.Asp1028His or p.D1028H, allele frequency 18%).

On the basis of this molecular profile, crizotinib (Xalkori, Pfizer) was initiated as part of the basket AcSé Crizotinib trial (NCT02034981). Crizotinib resulted in a 56% reduction in size of the target lesions that was followed by progression of the disease 10 months later (Fig. 1). The patient was then enrolled in the MATCH-R (A Prospective Trial to Study the Evolution of Clonal Architecture of Tumors from Patients Treated with Molecular Targeted Agents) trial at Gustave Roussy Cancer Campus, in which next-generation sequencing, comparative genomic hybridization, and patient-derived xenografts from tumors that progress during administration of targeted therapy (ID-RCB number: 2014-A01147-40) are performed. Biopsy of the progressing pulmonary lymph node (containing 70% tumor cells) revealed a novel *EGFR* amplification (log ratio 1.21) associated with an activating mutation of *EGFR* located in a hot spot codon of p.Leu861Arg

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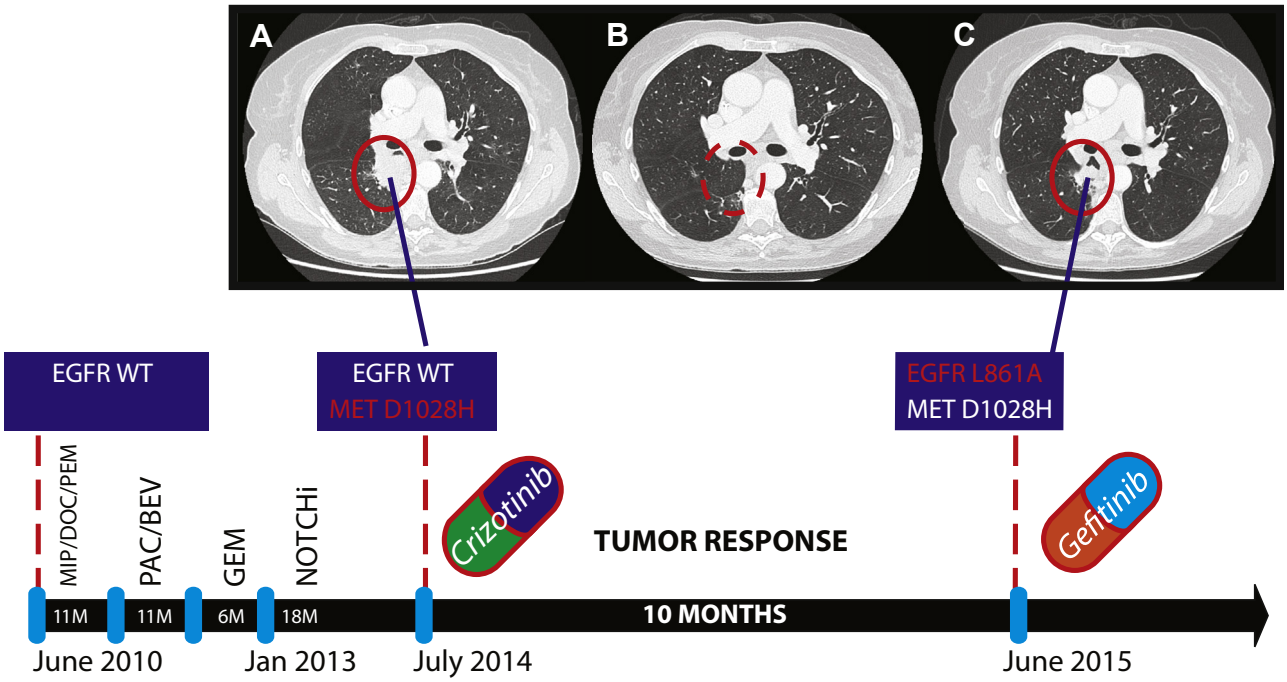

Figure 1. Patient 1: clinical course, including treatment history and relevant imaging studies and tumor biopsy specimens. Representative images from computed tomography of the chest at different times: (*A*) at baseline (before administration of crizotinib), showing right pulmonary lesion; (*B*) at 3 months, with an excellent tumor response in right pulmonary lesion; and (*C*) at 10 months, with tumor progression. Abbreviations: DOC, docetaxel; EGFR, epidermal growth factor receptor; GEM, gemcitabine; KRAS, Kirsten rat sarcoma viral oncogene homolog; M, months; MIP, mitomycin-ifosfamide-cisplatin; NOTCHi, inhibitor of the Notch pathway; PAC-BEV, paclitaxel-bevacizumab; PEM, pemetrexed; WT, wild-type.

(p.L861R, allele frequency 53%) activating mutation on exon 21. The p.D1028H *MET* mutation was still present (allele frequency 6%). Given this molecular profile and the patient's resistance to crizotinib, administration of the epidermal growth factor receptor (EGFR) inhibitor gefitinib was initiated.

Crizotinib is registered primarily for *ALK*-translocated non–small cell lung cancer. Therefore, most resistance

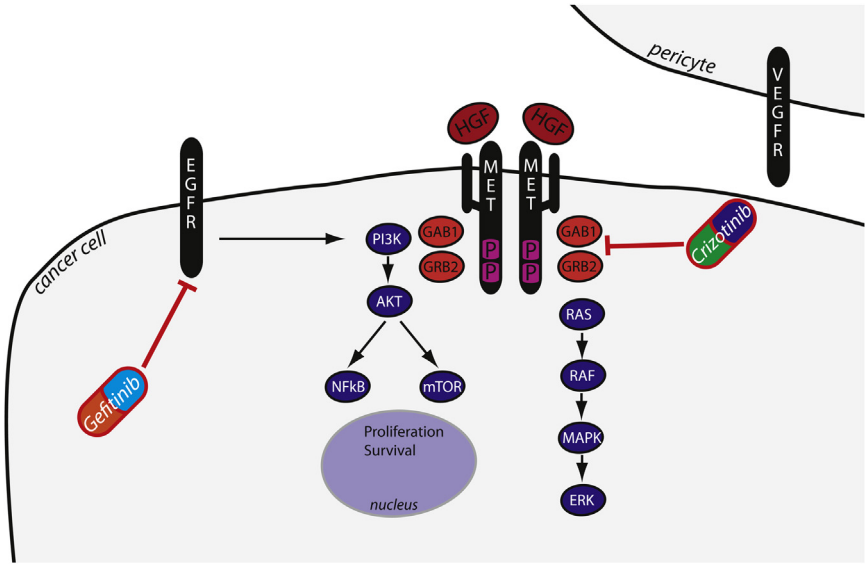

Figure 2. Signaling pathways activated by hepatocyte growth factor and MET. Cytoplasmic effector molecules, including growth factor receptor-bound protein 2 (GRB2) and GRB2-associated binding protein (GAB1) are recruited to the docking site. Abbreviations: AKT, protein kinase B; ERK, extracellular signal-regulated kinase; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycine; NfkB, nuclear factor kappa B; PI3K, phosphatidyl inositol 3-OH-kinase; VEGFR, vascular endothelial growth factor receptor.

mechanisms have been described in this context and include the following: secondary *ALK* mutations (28%), *ALK* copy number gain (18%), *EGFR* mutations (36%, mainly exon 20 p.S768I and exon 21 p.L858R mutations), and rare *KRAS* mutations.[3] Approximately one-fifth of the resistance mechanisms remain unknown. Interestingly, crizotinib was initially developed as a *MET* inhibitor,[4] and some clinical trials are still evaluating it for that indication (NCT00585195). *MET* exon14 alterations (4% of adenocarcinomas of the lung[5]) lead to crizotinib sensitivity.[6] Whether mechanisms of resistance to crizotinib used in a *MET*-mutated population are the same as those in an *ALK*-translocated population is still unknown (Fig. 2). Logic would suggest that they could be divided into two groups: specific resistance mechanisms (consisting of mutation of the kinase domain of the target of interest, ALK or MET, respectively), and common resistance mechanisms, which would include the activation of alternative pathways to bypass inhibition of the oncogenic driver. Interestingly, the *EGFR* mutation described here had not been observed previously in the crizotinib-resistant *ALK*-translocated population, which suggests greater "target specificity" of the resistance mechanisms.

This case also illustrates the challenges of tumors' temporal and spatial heterogeneity: the fact that despite a deep coverage of 3086 X at the corresponding position, the *EGFR* p.L861R mutation was not detected at the initiation of crizotinib therapy does not rule out the possibility that it was already present at another tumor location or at undetectable levels in a subclone.

In summary, here we have described a previously unreported EGFR activating hot spot mutation as an acquired mechanism of resistance to crizotinib in a *MET*-mutated non–small cell lung cancer tumor. This illustrates the importance of repeated molecular profiling in precision medicine.

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