Editorial Commentary

HER2-D16 oncogenic driver mutation confers osimertinib resistance in EGFR mutation-positive non-small cell lung cancer

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Epidermal growth factor receptor (*EGFR*) mutations are the most frequent drivers of tumor development among patients with non-small cell lung cancer (NSCLC) in Asian-Pacific countries. Several phase 3 trials have demonstrated that first-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) EGFR-tyrosine kinase inhibitors (TKIs) exhibit superior efficacy to standard platinum-based chemotherapy for treating patients with EGFR mutation-positive advanced NSCLC (1-3). Despite the remarkable success of EGFR-TKIs in clinical settings, with an objective response rate of 60–70%, the emergence of resistance remains a major limitation to therapeutic efficacy, with the average progression-free survival (PFS) ranging from 9 to 15 months (4). Development of the EGFR-T790M mutation in EGFR exon 20, which prevents the binding of first- and second-generation EGFR-TKIs to the ATP binding site, has been reported as the most common resistance mechanism (5). However, the third-generation EGFR-TKI osimertinib was developed for clinical use to overcome resistance (6). Currently, osimertinib, a mutant selective, irreversible EGFR-TKI, is approved for treating patients with EGFR-T790M-positive advanced NSCLC following treatment with first- and second-generation EGFR-TKIs and has been also approved as a first-line therapy for patients with EGFR mutation-positive advanced NSCLC regardless of their T790M mutation status (7). As an initial therapy, osimertinib resulted in a median PFS of 18.9 months (7). After the failure of previous EGFR-TKI therapy with EGFR-T790M mutation, osimertinib exhibited significantly greater efficacy than platinum-pemetrexed therapy. The median PFS was significantly longer with osimertinib than with platinum-pemetrexed (10.1 *vs.* 4.4 months). The objective response rate was significantly better with osimertinib than with platinum-pemetrexed (71% *vs.* 31%) (8). Therefore, osimertinib was approved for treating patients with EGFR-T790M-positive NSCLC following progression during prior EGFR-TKI treatment. However, all patients ultimately developed resistance to osimertinib in both in the first-line treatment setting and as a salvage therapy for EGFR-T790M-positive NSCLC. The mechanisms underlying resistance to osimertinib include a wide spectrum of aberrations, reflecting the molecular heterogeneity of NSCLC tumors.

Hsu *et al.* (9) recently described a human epidermal growth factor 2 (*HER2*) exon 16-skipping mutation in a patient with NSCLC also harboring EGFR-L858R/T790M mutations who acquired resistance to osimertinib. To determine the underlying mechanism linking *HER2* mutation with drug resistance, the researchers used an *in vitro* model of H1975 cells stably expressing high levels of *HER2* accompanied by an exon 16-skipping deletion (designated HER2-D16). The study showed that afatinib, a pan-HER inhibitor, overcame HER2-D16

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induced osimertinib-resistance by using a combination of osimertinib in a preclinical model of stably expressing HER2-D16-H1975 cells. Hsu *et al*. showed that combination treatment with osimertinib and afatinib, which inhibits HER2 activation, suppressed the proliferation of HER2-D16-mutant cells. This study supports HER2-D16 emergence causing bypass signals in clinical samples, providing insight into targeted treatment for HER2-mutated solid tumors, including NSCLC.

HER2 (also known as erbB-2/neu) is a member of the erbB receptor tyrosine kinase family and is encoded by *ERBB2*, a major proliferative driver that activates downstream signaling through the PI3K-AKT and MEK-ERK pathways. No ligand has been described for this receptor, which is activated by homodimerization or heterodimerization with other members of the erbB family. *HER2* alterations have been identified as oncogenic drivers and potential therapeutic targets in lung cancers (10,11); *HER2* mutations and amplification have been reported in approximately 2–3% and 2–5% of lung adenocarcinomas, respectively (12,13). Interestingly, HER2 mutation is more commonly associated with a selected subgroup of women and never-smokers harboring tumors with an adenocarcinoma histology (14). Similar findings were reported for subpopulations of patients with lung cancers harboring EGFR mutations (15), suggesting that similar genetic factors, carcinogens, or environmental factors affect the occurrence of mutations in both EGFR and HER2. However, no specific therapeutics targeting HER2 amplification or mutations have been developed.

The resistance mechanisms to EGFR-TKIs can be broadly divided into five groups: secondary mutations in EGFR (e.g., T790M, C797S), bypass signaling activation (e.g., HER2, AXL, cMET), activation of downstream molecules (e.g., *PIK-3CA* mutation, *PTEN* loss, *BRAF* mutation), phenotypic transformation (e.g., small cell lung cancer, epithelial-mesenchymal transition), and resistance to apoptotic cell death (e.g., *BIM* polymorphism) (16). An increased *HER2* copy number has also been associated with a poor therapeutic response to EGFR-TKIs in patients with lung cancer (17). Using clinical samples and preclinical models with acquired resistance to EGFR-TKIs, HER2 amplification was detected along with the loss of EGFR-T790M mutation, indicating that HER2 amplification and EGFR-T790M are mutually exclusive (18,19). *HER2* amplification was detected in approximately 10% of cases exhibiting EGFR-TKI resistance but in only 3% of cases without prior EGFR-TKI treatment (20). *HER2* mutation causing an exon 20 insertion was detected in the circulating tumor DNA of the plasma from a patient who acquired resistance to osimertinib (21). The most common *HER2* mutation consists of a 12-base pair (bp) insertion in exon 20, resulting in addition of the amino acid residues YVMA. However, *HER2* amplification does not typically coexist with *HER2* mutations (20).

Hsu *et al*. first identified the novel HER2-D16 mutation as a deletion in exon 16 in a patient with EGFR-L858R/T790M-positive NSCLC (9). Alternatively, in breast cancer, the HER2-D16 mutation was recognized as a crucial driver of aggressive behaviors of HER2-positive tumors and was significantly associated with locally disseminated lymph nodes-positive breast cancer (22). Moreover, amplified HER2-D16-driven oncogenic signals were associated with the downstream oncogenic SRC signal transduction pathway. This HER2-D16–SRC axis has also been shown to be activated in mammary adenocarcinomas from genetically engineered cell lines and in HER2-positive breast cancer tissues from patients (22,23). Therefore, activated SRC is the key surrogate marker of HER2-positive breast cancer, which acts downstream of the oncogenic HER2-D16 signal. However, in this new study in a HER2-D16-expressing NSCLC cell model, Hsu *et al*. (9) demonstrated that signal transduction of HER2-D16-driven resistance to osimertinib occurred independently of SRC. This model was established from H1975 cells expressing EGFR-L858R/T790M, which were then transfected with plasmids encoding HER2-D16, followed by the selection of stable clones, resulting in cells expressing the dual driver mutations EGFR-L858R/T790M and HER2-D16. These dual driver mutations cooperatively influenced the downstream signal transduction pathway in this model. All *HER2* mutations were mutually exclusive with other driver mutations in *EGFR*, *KRAS*, *BRAF*, *NRAS*, *PI3KCA*, *MEK*, and *AKT*, as well as *ALK* rearrangements. Accordingly, whether EGFR-L858R and EGFR-T790M mutations coexist with HER2-D16 in the same tumor remained unclear. The EGFR-L858R/T790M and HER2-D16 mutations may have existed in different tumor cells in this patient.

Hsu and colleagues further observed loss of EGFR-T790M following osimertinib treatment from cell-free DNA of the patient, whereas the expression level of HER2-D16 was increased. Osimertinib treatment failed in this patient. Interestingly, the expression of EGFR-T790M and HER2-D16 were exclusive and showed an opposite relationship with the response to osimertinib, whereas the expression level of EGFR-L858R did not

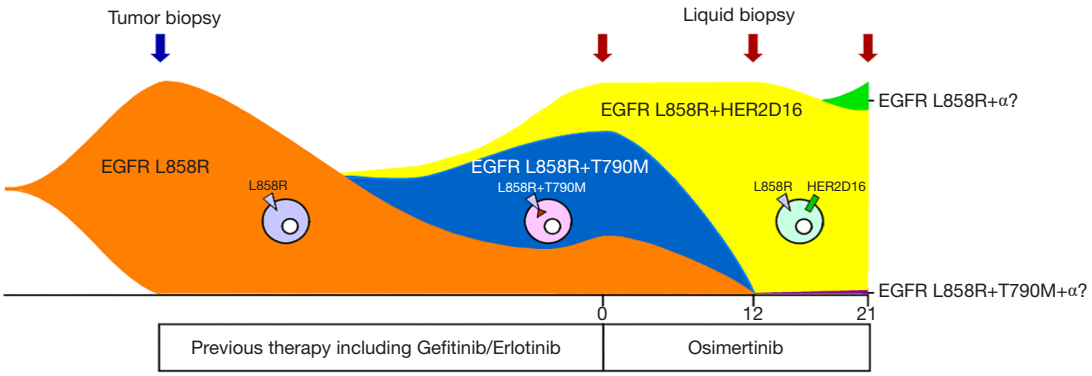

Figure 1 Possible clonal selection mechanism of this lung cancer.

change during osimertinib treatment based on plasma cell-free DNA analysis. A similar loss of the target EGFR mutation by EGFR-TKI treatment has been reported in both preclinical and clinical studies (24). We also reported loss of an EGFR-activating mutation (15-bp deletion in *EGFR* exon 19: EGFR-ex19del) in an afatinib-resistant cell line (25). Similar results were reported for the loss of mutant alleles from gefitinib- and erlotinib-resistant PC-9, HCC827, and 11-18 cells, which also involved bypass of the signal transduction pathway to HER2, ERBB3, or IGF1R, or induction of epithelial-mesenchymal transition with stem cell-like properties (26,27). Moreover, loss of EGFR-activating mutations was observed in clinical samples from patients who were refractory to EGFR-TKI treatment (26). Recently, wild-type *EGFR* amplification was observed in PC-9 cells resistant to the third-generation EGFR-TKI rociletinib harboring an exon 19 deletion in *EGFR* and in clinical tissue samples from patients after the failure of rociletinib treatment (28,29).

In the study by Hsu *et al.* (9), the patient's right lung tumor harbored the EGFR-L858R mutation, and thus gefitinib treatment was initiated; however, his disease progressed within only 4 months of treatment. The regimen was then switched to cisplatin-pemetrexed chemotherapy, erlotinib, paclitaxel, gemcitabine, and vinorelbine continuously. Despite treatment, a malignant pleural effusion developed, which showed an EGFR-L858R mutation in exon 21 and EGFR-T790M mutation in exon 20. These two EGFR mutations along with the HER2-D16 mutation were detected in plasma cell-free DNA before osimertinib treatment. This suggests the existence of at least three types of clonal cells in tumors expressing EGFR-L858R, EGFR-L8578R/T790M, and EGFR-L858R + HER2-D16 (*Figure 1*). Thus, osimertinib treatment selected tumor cells expressing EGFR-L858R + HER2-D16, as these cells were not effectively suppressed by the treatment, whereas cells expressing EGFR-L858R and EGFR-L858R/T790M were decreased. This may further explain why the cells expressing EGFR-L858R were not decreased based on analysis of plasma cell-free DNA. Specifically, prior to gefitinib treatment, most tumor cells may have harbored the EGFR-L858R mutation; however, during treatment with the first-generation EGFR-TKIs gefitinib and erlotinib, the tumor cells acquired the EGFR-T790M along with the EGFR-L858R mutation because of the adaptation of selective pressure or spontaneous evolutionary emergence. Therefore, based on cell-free DNA analysis, at the time of initial treatment of osimertinib, it is possible that at least three types of EGFR/HER2-mutated tumor cells may have co-existed in the same tumor, including EGFR-L858R, EGFR-L858R/T790M, and EGFR-L858R + HER2-D16. Thus, osimertinib completely suppressed tumor cells expressing EGFR-L858R and EGFR-L858R/T790M, leaving only those expressing EGFR-L858R + HER2-D16. Although these EGFR-L858R and HER2-D16 driver mutations may have exclusive effects and mechanisms, they may exist in the same tumor cells. Indeed, the expression levels of EGFR-L858R and HER2-D16 were very similar, with 79% and 80% positivity at 12 weeks and 82% and 70% positivity at 21 weeks of osimertinib treatment, respectively, further supporting that these mutations coexisted in the same tumor cells.

Nakatani *et al.* (30) reported that treatment with rociletinib, a third generation EGFR-TKI, suppressed the proliferation of afatinib-resistant PC-9 cells expressing EGFR ex19del/T790M. Rociletinib-resistant cell lines were

then established by 10–12-month exposure to progressively increasing concentrations of rociletinib. Allelic quantitative distribution analysis using EGFR mutation-specific droplet digital PCR showed that the EGFR ex19del and EGFR-T790M alleles were substantially decreased in these rociletinib-resistant cell lines (named RocR1 and RocR2 cells). Because the third-generation EGFR-TKIs rociletinib and osimertinib are EGFR mutation-selective inhibitors, suppression of the expression of the target EGFR ex19del/T790M along with amplification of wild-type EGFR in RocR1 and RocR2 cells led to the use of bypass signal pathway(s) for cell survival. Therefore, the lack of a change in the expression level of EGFR-L858R during osimertinib treatment observed by Hsu *et al*. (9) is intriguing, as the expression of EGFR-T790M was attenuated whereas HER2-D16 expression was increased. These results further suggest that EGFR-L858R coexisted with both EGFR-T790M and HER2-D16 in the same tumor cells in the patient. These findings have clinical applications, highlighting the importance of repeated analyses of EGFR mutation status during EGFR-TKI treatment.

This study further demonstrated that suppression of HER2D16 activation by afatinib, a pan-HER inhibitor, in combination with suppression of EGFR-L858R/T790M by osimertinib had a synergistic effect on the resistance conferred by these two mutations. Interestingly, the inhibitory effect of trastuzumab for HER2D16 in breast cancer is controversial because conflicting results have been observed between *in vitro* and *in vivo* studies (22,23). In breast cancer, HER2-targeted therapies have significantly improved the survival of patients with HER2-positive tumors as an adjuvant/neoadjuvant treatment and in metastatic cases. In gastric cancer, HER2-targeted therapy of a trastuzumab-based regimen was also approved for HER2-positive, previously untreated metastatic gastric cancer (31). In these cases, "HER2-positive" is determined based on an immunohistochemical staining score of 3+ in biopsy or surgically resected tumor samples. Combination treatment of trastuzumab and pertuzumab, as dual anti-HER2 humanized monoclonal antibodies, with chemotherapy is recommended as a first-line therapy for metastatic breast cancer. Other HER2-target therapies such as the HER2 kinase inhibitor lapatinib and antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1) can be used as subsequent treatment options. However, there is currently no approved targeted therapy for solid tumors with HER2 mutations, including breast cancer, NSCLC, gastric cancer, or colon cancer. Moreover, patients with HER2 mutations show a worse prognosis patients with lung adenocarcinomas containing other oncogenic drivers (32). Therefore, effective therapeutics for patients with HER2 mutations are required.

Recently, the clinical effects of the novel ADC trastuzumab deruxtecan (T-DXd; DS-8201a) were reported in a phase I trial of patients with HER2-expressing non-breast and non-gastric cancer or HER2-mutant solid tumors (33). T-DXd is a humanized anti-HER2 antibody with a cleavable, peptide-based linker, and potently inhibits topoisomerase I. In this trial, patients with HER2-mutant NSCLC had more pronounced tumor shrinkage than those with wild-type HER2-expressing NSCLC, with an objective response rate of 72.7% (8/11) and median PFS of 11.3 months (95% confidence interval 8.1–14.3 months). The safety profile was generally acceptable. Among the 11 patients with NSCLC with HER2 mutations enrolled in the study, eight had kinase domain mutations, two had transmembrane domain mutations, and one had extracellular domain mutations; however, no patient with NSCLC harbored the HER2-D16 mutation. Li *et al*. (34) demonstrated that HER2-activating mutations facilitated receptor ubiquitination and internalization, resulting in enhanced sensitivity to anti-HER2 ADCs such as T-DM1 and T-DXd in lung cancer based on preclinical models and clinical samples. Furthermore, a pan-HER irreversible inhibitor such as neratinib or afatinib enhanced internalization of the HER2-ADC complex by increasing HER2 ubiquitination through inhibition of HSP90 activity. *In vivo* efficacy evaluation showed that both T-DM1 alone and the combination of T-DM1 and neratinib induced marked tumor regression in an *ERBB2* S310F mutant PDX model, although the effect was more durable with combined treatment. However, there are no current clinical trials evaluating the clinical benefit of the combination of T-DM1 and a pan-HER irreversible inhibitor in patients with *ERBB2*-mutant lung cancer.

Overall, Hsu *et al*. (9) demonstrated the potential of combining osimertinib and afatinib for treating NSCLC with EGFR-L858R/T790M and HER2D16 mutations in a preclinical model. As mentioned above, this *in vitro* H1975 cell model, expressing both EGFR-L858R/T790M + HER2D16, is an exceptional case and may differ from the patient's mutation profile, indicating that the tumor expressed EGFR-L858R + HER2D16 in plasma cell-free DNA analysis. This is consistent with the exclusive relationship between EGFR-T790M and HER2 mutation/amplification. It may be useful to treat the model of EGFR-L858R + HER2D16 with afatinib as a single agent,

providing additional potential therapeutics for patients with EGFR mutation-positive NSCLC. This new study along with the findings summarized should be further evaluated by HER2 mutation analysis and to evaluate HER2 inhibitor strategies using optimal drugs and drug combinations to enable precision medicine for HER2-mutated lung cancer using a molecular-targeted and rational approach. Furthermore, during treatment with EGFR-TKIs, repeated analysis of oncogenic driver mutations using plasma cell-free DNA would be essential for ensuring the effectiveness of therapeutics even after acquiring resistance in patients with EGFR mutation-positive NSCLC.

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