Lung cancer remains a leading cause of cancer-related mortality in both male and female worldwide. Non-small cell lung cancer (NSCLC) including adenocarcinoma, squamous cell carcinoma and large cell carcinoma constitutes the majority of lung cancer (~85%) cases. As a result of the technical advance and the availability of targeted drugs, systematic testing for major gene mutations has become standard of care for clinical decision-making.

The ErbB receptor tyrosine kinase family consists of four cell surface receptors: ErbB1/EGFR/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4. These receptors share structural homology and are prototypical cell membrane receptor tyrosine kinases that are activated following ligand binding and receptor dimerization (1). HER2 exon 20 insertion is an independent driver mutation in NSCLC (2) and HER2 gene amplification in NSCLC is associated with acquired resistance to EGFR-targeted therapy (3). HER2 amplification is found in approximately 2–4% of NSCLCs (4) and HER2 gene mutation occurs in approximately 2–5% of NSCLCs (2). Targeting these HER2 alterations in NSCLC remains a challenge as compared to the success recorded against the alterations in EGFR and ALK1 mutations calling for more efforts in this field.

Effective HER2-directed therapies (e.g., trastuzumab and lapatinib) that are currently used to treat breast cancer patients have not been as effective in NSCLC with HER2 genetic alterations (10,11). Pillai et al. reported that patients receiving HER2-directed therapy had a median survival of 2.1 years compared with 1.4 years for those who did not, a promising but not significant finding due to a small sample size (12). Similarly, results from the European EUHER2 cohort showed similar response rates and progression-free survival (PFS) in NSCLC patients with HER2 mutations when treated with HER2-directed therapy versus chemotherapy (13). Currently a few clinical trials are ongoing to test HER2-directed therapy in NSCLC.

At the bench, a major challenge to test HER2-directed therapies in NSCLC is the lack of sufficient numbers of human NSCLC cell lines with HER2 aberrations and in vivo models that could faithfully replicate the experience in the clinical settings. In the current article by Liu et al. (14), the efficacy of osimertinib in targeting HER2 aberrations in preclinical lung cancer mouse models was studied. The
authors generated and validated three engineered mouse models that mimic human NSCLC driven by aberrant HER2 including HER2 amplification alone (HER2wt), HER2 amplification with sensitizing EGFR mutation (HER2mu/EGFRwt) and activating HER2 exon 20 insertion (HER2mu). These mouse models come in handy as valuable tools for the development and evaluation of HER2-targeted therapies in the preclinical setting.

Osimertinib and its active metabolites inhibit other kinases including HER2/HER4, ACK1, ALK, BLK, BRK, MLK1, and MNK2 in vitro at high concentration (e.g., 1 mM) (5). In the study by Liu et al. (14), the authors showed that osimertinib at concentrations ranging from 0.1 to 1 mM was capable of targeting HER2 by suppressing its phosphorylation in murine Ba/F3-HER2wt cells stably expressing wild-type human HER2. Importantly, osimertinib treatment significantly reduced tumor sizes in mice bearing tumors driven by HER2wt and HER2mu/EGFRwt accompanied by decreased phospho-HER2 levels and other major downstream signaling targets such as p-AKT and p-ERK levels in the harvested tumor tissues, consistent with in vitro data. The authors ascribed these changes to on-target effect of osimertinib against HER2 in these tumors. It is well known that the initial target of osimertinib is EGFR (primarily mutant EGFRs). It is possible that osimertinib is effective when wild-type HER2 binds with EGFR and activates signaling pathways downstream of their heterodimer formation. It has been shown that HER2 is the preferred partner for binding with EGFR and that the EGFR/HER2 heterodimer possesses higher potential for signaling than EGFR homodimers (15). If osimertinib indeed inhibits HER2 signaling through suppression of the EGFR/HER2 heterodimer, we reasonably assume that much higher concentration or dosage of osimertinib may be needed to exert inhibitory activity against EGFR/HER2 heterodimer over mutant EGFRs given that osimertinib has limited activity against wild-type EGFR and particularly HER2. In the current study, doses lower than 25 mg/kg e.g., 1–10 mg/kg, which showed efficacy against EGFRm NSCLC tumors (5), were not tested or shown to have a similar antitumor activity.

Surprisingly, erlotinib, a first-generation EGFR-TKI, failed to show anti-tumor effects in these two models (i.e., with HER2wt and HER2mu/EGFRwt). Since erlotinib has greater potency than osimertinib against wild-type EGFR, it would be expected to be more effective than or at least as potent as osimertinib in inhibiting EGFR/HER2 heterodimer. In agreement, erlotinib failed to suppress phosphorylation of HER2, Akt and ERK in HER2wt in harvested tumor tissues. Moreover, afatinib, a second generation EGFR-TKI with dual inhibitory activity against both EGFR and HER2, also showed limited activity against HER2wt tumors. Therefore, it is not clear whether inhibition of the EGFR/HER2 heterodimer accounts for the potent efficacy of osimertinib against HER2-driven tumors. The study failed to provide a mechanistic insight on how osimertinib suppresses HER2 signaling and HER2wt tumors through the expected “on-target” effect.

In contrast to the findings in HER2wt and HER2mu/EGFRwt models, HER2 exon 20 insertion-driven NSCLC (HER2mu) did not respond to osimertinib. It has been demonstrated that HER2 mutation has distinct clinical features as compared to HER2 amplification-driven NSCLC (16,17). A previous study showed that activating HER2 mutation in exon 20 possesses enhanced transforming capacity than its wild-type counterpart in normal human bronchial and mammary epithelial cells. Moreover, HER2 mutation can transphosphorylate both WT and kinase dead (K721R) EGFR in the presence of EGFR-TKIs including erlotinib and gefitinib in vitro (18). In addition, siRNA targeting HER2 mutation resensitized the cells to these EGFR-TKIs, suggesting that HER2 mutation counteracts the activity of EGFR-TKIs. These findings may explain why osimertinib is futile against tumors driven by HER2 mutation.

JQ1 is a BET inhibitor with demonstrated anti-tumor effects in a variety of cancers including multiple myeloma, lung adenocarcinoma, and pancreatic ductal adenocarcinoma (19). This study for the first time demonstrates that the combination of osimertinib and JQ1 significantly decreased tumor growth of NSCLC driven by HER2mu and enhance survival in vivo (14), warranting future clinical evaluation of this combinational strategy against NSCLC with HER2 mutation. It would be nice if the authors had evaluated the efficacy of the combination in HER2wt and HER2mu/EGFRwt models. Disappointingly, this study did not clearly delineate the mechanism underlying the synergistic effects between osimertinib and JQ1 against HER2 mutation-driven NSCLC tumors, which is likely complex, but worthy of further investigation.

This study by Liu et al. (14) clearly shows that osimertinib is robustly active in HER2wt and HER2mu/EGFRmu as a single agent, but not in HER2mu-driven NSCLC model, highlighting the importance of deciphering different HER2 aberrations for the proper application of HER2-directed therapies in the clinic. Further preclinical
and clinical validation of osimertinib for the treatment of NSCLCs with HER2 aberrations either as a single agent or combined with other agents such as BET inhibitor, is needed in order to establish osimertinib as a treatment option for NSCLCs with HER2 aberrations.

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Footnote

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