



An expanding role for osimertinib for the treatment of ErbB family driven NSCLC

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The discovery that a subset of non-small cell lung cancers (NSCLC) were dependent upon reoccurring activating *EGFR* (*ErbB1*) mutations (1-4), primarily deletions of exon 19 or an activating point mutation, *L858R*, ushered in the era of targeted therapies for lung cancer. Shortly after, first-generation *EGFR* tyrosine kinase inhibitors (TKIs) that were capable of inhibiting these mutant proteins proved effective. However, the enthusiasm was hampered by the clinical appearance of acquired resistance mediated by a secondary *EGFR* mutation, converting threonine at position 790 to methionine (T790M) (5), in effect, blocking the ability of the inhibitor to access the ATP binding pocket of *EGFR*.

It was later determined that almost half the cases of *EGFR* inhibitor resistance are caused by the acquisition, or enrichment from a small percent of alleles present prior to initiation of treatment, of T790M (6). This led to the subsequent development of next-generation *EGFR* inhibitors, with third-generation *EGFR* inhibitors like osimertinib (AZD9291) demonstrating efficacy in *EGFR* mutant NSCLCs with acquired T790M mutations (7,8). More recently, the FLAURA investigators compared osimertinib with 1st generation *EGFR* TKIs (erlotinib and gefitinib) in treatment-naïve *EGFR* mutant advanced NSCLC (9). Strikingly, patients treated with osimertinib demonstrated a median duration of response of 17.2 months compared to 8.5 months for 1st generation *EGFR* TKIs. Furthermore, there was an improved toxicity profile with osimertinib. There have been other impressive responses to osimertinib in the first-line therapy for patients with

de novo T790M mutations as well, further demonstrating the potential of the drug (10). The FLAURA study has resulted in the adoption of osimertinib as the preferred first-line therapy for *EGFR* mutant lung cancer based on its improved efficacy and favorable toxicity profile. However, it remains to be known whether overall survival of these patients will exceed or fall short of those who receive first-line *EGFR* inhibitors until the acquisition of T790M, and then receive osimertinib.

The role of other ErbB members in *EGFR* mutant NSCLC

EGFR also known as *ErbB1* is part of a four-member family of transmembrane proteins, along with *ErbB2* (HER2), *ErbB3*, and *ErbB4* (11). While *EGFR* is actionable in lung, glioma, head and neck and colorectal cancer, HER2 is a prominent drug target itself, particularly in breast cancer (12) and gastric cancer (13), but does have an established role in lung cancer as well. Interestingly, one of the earliest cell lines found to respond *in vitro* to gefitinib was NCI-H1819 (14), which is *EGFR* wild-type but HER2-dependent. In 175 lung adenocarcinomas, Li and colleagues (15) found that HER2 was both amplified and mutated at a rate of ~3%, and these alterations were found independent of each other. HER2 has also emerged as an important modulator of *EGFR* inhibitor response in cancer, including *EGFR* amplified colorectal cancer and *EGFR* mutant NSCLC (16). Pao and colleagues demonstrated that *HER2* is amplified in ~10%

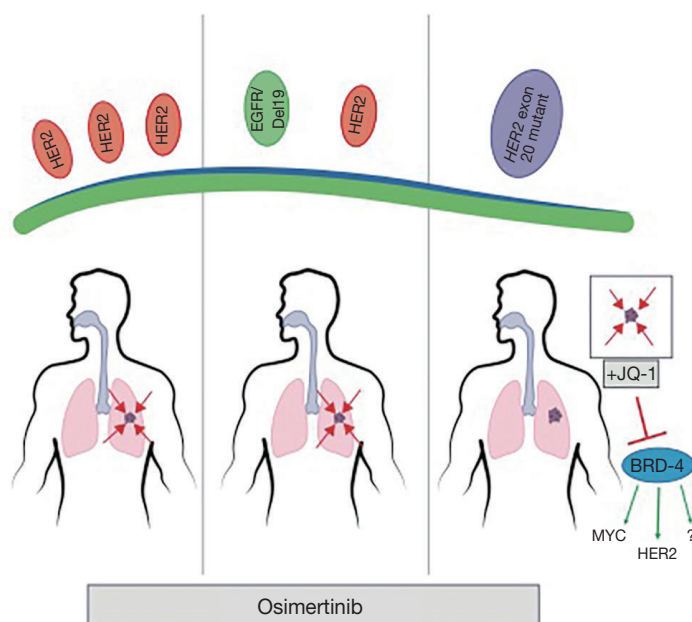


Figure 1 Genetically-distinct NSCLCs have sensitivity to osimertinib-based therapies in mouse models. NSCLC tumors are depicted with HER2 overexpression (left), HER2 overexpression coupled with an activating *EGFR* exon 19 deletion mutation (middle), or with *HER2* exon deletion mutations (right). In the first two cases, these tumors respond well to osimertinib in GEMMs of NSCLC. While *HER2* exon deletions are insensitive to single-agent osimertinib (right), these tumors are sensitized by the addition of the BET inhibitor, JQ-1, which inhibits bromodomain-containing proteins such as bromodomain-containing protein-4 (BRD4). This leads to decreased HER2 and MYC expression as well as other potential oncogenic drivers leading to synergistic activity of the combination *in vivo*.

of patients with acquired resistance to EGFR inhibitor, compared to 1% of EGFR inhibitor treatment-naïve *EGFR* mutant NSCLCs (17). Furthermore, HER2 amplification was independent of T790M mutations in the acquired resistant tumors (17).

Clinically, responses of HER2-altered NSCLCs to both HER2 inhibitors and EGFR inhibitors have been mixed. De Grève reported the pan- and irreversible ErbB inhibitor afatinib led to objective responses in three out of three *HER2* mutant metastatic NSCLC patients (18). Dacomitinib, a similar second generation pan-inhibitor of the ErbB family (other than ErbB3), resulted in 3 partial responses out of 26 patients (19). More recently, the HER2 antibody-drug conjugate, ado-trastuzumab emtansine (20), demonstrated a partial response rate of 44% in 18 patients, with a median survival of 5 months. Responses were seen in a number of different mutations, and also in patients with *HER2* exon 20 insertions. While these responses were relatively short-lived, it is significant that both a large subset of patients responded across a broad range of HER2 alterations.

Despite the responses elicited by ado-trastuzumab emtansine (20), it is clear that a better understanding of the molecular and biological characteristics of the different HER2 alterations, both alone and in the presence of *EGFR* mutations, that are seen across the NSCLC landscape, would aid in finding the best available inhibitor to treat each NSCLC molecular subtype and hopefully result in more durable responses.

To this point, Liu and colleagues (21) directly tackled this question by testing discrete HER2 alterations in NSCLC and the therapeutic efficacy of osimertinib against each alteration in mouse models (*Figure 1*). The researchers tested osimertinib against three molecularly distinct HER2 altered NSCLCs: (I) *HER2* overexpressed NSCLC; (II) *EGFR*del19/*HER2* overexpressed NSCLC; and (III) *HER2* exon 20 insertion in mouse NSCLC models. The animal experiments were performed using several unique models of NSCLC genetically engineered mouse models (GEMMs). Therefore, these authors were uniquely positioned to be able to robustly study the biology and therapeutic responses of these cancer types.

First however, the authors confirmed the increased efficacy of osimertinib against HER2 compared to other EGFR TKIs by demonstrated that the HER2 overexpressing Ba/F3 cells had significantly lower GI50s (10.4 nM), than erlotinib (438 nM), underlying the ability of osimertinib to potently inhibit HER2. They next turned to their GEMM model of HER2 overexpressing NSCLC. Interestingly, the authors demonstrated that overexpressing HER2 was sufficient to drive high-grade adenocarcinoma formation. Importantly, these tumors uniformly shrank following osimertinib treatment but were resistant to either erlotinib or the pan-HER TKI, afatinib, demonstrating *in vivo* that osimertinib is uniquely effective against HER2 overexpressing NSCLC.

Next, the authors looked at the effects of HER2 overexpression on EGFR mutant deletion 19 tumors, a combination found in ~10% of EGFR mutant NSCLC with acquired resistance to first generation TKIs (17). Again, they employed a unique GEMM model that both expressed the mutant EGFR and overexpressed HER2. While the survival of these mice was extended by 2 weeks with erlotinib, the survival of osimertinib-treated mice was 24 weeks, with several of these mice surviving the experiment. These data demonstrate that in the second tested NSCLC subtype, osimertinib was also active.

The authors then turned their attention to HER2 exon 20 mutant NSCLCs. First, by expressing the most frequent HER2 exon 20 insertion mutation (*A775_G776insYVMA*) in Ba-F3 cells, the investigators demonstrated, similarly to the HER2-overexpressing Ba/F3 cells, osimertinib was sufficient to inhibit these cells. However, the amount of osimertinib to reach GI50 levels was about 4 times greater than what was required in HER2 wt cells. These data proved to portend the results of osimertinib treatment in a GEMM of HER2 exon 20 mutant (*A775_G776insYVMA*) NSCLC, as these mice responded poorly to osimertinib and experience no improvement in survival. Interestingly, the investigators had previously demonstrated that afatinib, which was less effective than osimertinib in their HER2 overexpression model, was effective in the HER2 exon 20 mutant model alone or in combination with rapamycin (22). It is unclear, why these EGFR TKIs display HER2 alteration subtype efficacy but deserves further investigation. The lack of activity of HER2 exon 20 mutant NSCLC is also consistent with a recent study demonstrated that the development of HER2 exon 20 mutations as mechanism of acquired resistance to osimertinib in patients with EGFR mutant NSCLC (23).

The authors then asked, given the *in vitro* signal from osimertinib, would a rationally-implemented second drug be sufficient to sensitize osimertinib in the HER2 exon 20 deletion model. To inform of this second drug, the authors noted signaling changes following osimertinib treatment in one of the only HER2 mutant NSCLC cell lines—NCI-H1781—which contains a rarer HER2 20 insertion mutation. They found a convergence in osimertinib inhibited signaling to two targets of the BET inhibitor JQ-1, p21 and c-MYC (24). The authors then tested the combination in the GEMM, and, impressively, found that while neither single-agent had significant activity, the combination led to profound survival increases in the mice.

Overall, the study by Wong and colleagues adds to the growing understanding that HER2 can be a successfully druggable target in NSCLC, both in the absence and presence of EGFR mutations. It also demonstrates the power that GEMMs afford to study cancers with relatively low frequencies and/or those with a lack of available established cell lines. Interestingly, some of these same authors recently demonstrated that while osimertinib is ineffective in HER2 mutant NSCLCs harboring exon 20 mutations, the less structurally cumbersome pan-ErbB inhibitor poziotinib is effective (25). In combination with the promising clinical data emerging with ado-trastuzumab emtansine (20), there are now several FDA-approved agents, albeit some approved for other indications, which can now be tested in HER2 altered NSCLC subtypes.

Lastly, the authors demonstrate a rationale combination of osimertinib with the BET inhibitor, JQ-1, for exon 20 deletion HER2 NSCLCs. As the authors point out, this is also interesting for the reason that exon 20 deletion EGFR NSCLCs are structurally analogous, make up 4–10% of EGFR mutant NSCLCs, and are irresponsive to traditional EGFR inhibitors (26). Thus, testing the combination of osimertinib/JQ-1 in EGFR exon 20 deletion NSCLCs may be the next step in further delineating promising strategies to treat EGFR and HER2 altered NSCLCs. This study also raises the question of how BET inhibitors resensitize to osimertinib in HER2 exon 20 mutant NSCLC. Although the authors demonstrated that JQ1 treatment lead to decrease HER2 and MYC expression, it is still unknown whether if modulation of these pathways is responsible for the observed *in vivo* synergy between osimertinib and JQ1. Several recent studies have shown that Bromodomain-containing protein-4 (BRD4), a key target of BET inhibitors, is critical for the upregulation of oncogenic RTKs in the setting of acquired resistance to PI3K, HER2,

and EGFR inhibitors (25,27,28). Therefore, future studies both in the laboratory and clinic will be necessary to define whether the critical target BET inhibitors when combined with a targeted agent is the primary RTK, a secondary or bypass RTK (such as MET), or downstream signaling pathway (such as MYC). These studies may not only lead to better treatment of HER2 altered NSCLC subtypes but may lead to novel upfront combinations for *EGFR* mutant NSCLC that may prevent or delay the development of resistance to osimertinib.

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