Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is the standard therapy for non-small cell lung cancer (NSCLC) harboring EGFR mutations, but the resistance is inevitable. The drug-tolerant persister cancer cells are thought to be involved in the resistance. We recently reported that HER2 expression had a negative impact on time-to-treatment-failure in patients with EGFR mutant NSCLC. In this study, we hypothesized that HER2 might be a potential target for alternative combination therapy in NSCLC harboring EGFR mutations. *In vitro* study showed that the level of HER2 expression had no correlation with the sensitivity to EGFR-TKI, erlotinib but showed some correlation with HER2-inhibitor, ado-trastuzumab emtansine (T-DM1) in multiple EGFR-mutant lung cancer cell lines. In addition, HER2 expression was increased in persister cancer cells in 11-18 cell line harboring EGFR L858R or HCC827 cell line harboring EGFR exon 19 deletion after the exposure to erlotinib *in vitro* and *in vivo*. The combination of erlotinib and T-DM1 showed a superior inhibitory effect on cell proliferation compared with those of the erlotinib or T-DM1 alone in either 11-18 or HCC827 cells *in vitro*. The combination therapy also induced a significantly greater inhibitory effect on tumor growth in xenograft model in mice transplanted with either 11-18 or HCC827 cells compared with erlotinib alone or T-DM1 alone. No body weight loss was observed in these mice. These results suggested that the combination therapy with EGFR-TKI and T-DM1 might be a potentially promising strategy for treating lung cancer harboring EGFR mutations.