Discovery of Epidermal Growth Factor Receptor (EGFR) Inhibitors.

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Genotype-directed targeted therapy is now the standard of care for subsets of patients with advanced non-small cell lung cancer (NSCLC). Especially, the discovery of activating mutations in EGFR, detected in 10-30% of NSCLC patients, has revolutionized the treatment of this disease. In the past decade, EGFR tyrosine kianse inhibitors (TKIs) including gefitinib, erlotinib, afatinib and osimertinib have been well developed for patients with advanced EGFR mutant lung cancer. However, EGFR-dependent NSCLC is still incurable because patients inevitablely develop acquired drug resistance, most frequently owing to the secondary T790M mutation within the ATP site of the receptor. Recently approved EGFR inhibitor, osimertinib that is an irreversible EGFR inhibitor, is highly potent against T790M mutant while sparing wild-type EGFR of which inhibition causes dose-limiting toxicities. However, its efficacy can be blunted by another acquired mutation at Cys797 that forms a covalent bond with osimertinib.

Moreover, there are relatively rare EGFR activating mutations including exon 20 insertion (Ex20Ins) mutations that are the third most common EGFR activating mutations in NSCLC, which collectively account for approximately 4% to 10% of all EGFR mutations. Patients with NSCLC harboring various Ex20Ins mutations rarely respond to treatment with the approved EGFR inhibitors, gefitinib, erlotinib or afatinib.

Collectively, a new class of inhibitors that can efficiently inhibit various EGFR mutations is urgently needed.