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Discovery and Development of Pyrotinib: a Novel Irreversible EGFR/HER2 Dual Tyrosine Kinase Inhibitor with Favorable Safety Profiles for the Treatment of Breast Cancer

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Abstract

The discovery and development of a novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor SHR1258 (pyrotinib) for the treatment of HER2-postive breast cancer is presented. The structure-activity relationship of lead series and their pharmacokinetic properties were evaluated to identify the potential candidates for further *in vivo* efficacy studies and preclinical safety assessments. Metabolic pathway and drug-drug interaction were also investigated in preclinical settings. In particular, major metabolites in human and animal species were assessed with regard to potential toxicity or off-target side effects. Overall, the potent and selective EGFR/HER2 dual inhibitor, pyrotinib, displayed robust anti-tumor effects on HER2-overexpressing xenograft models and sufficiently safety windows in animals as well as favorable pharmacokinetic properties in human, which substantially ensures current clinical development. Finally, recent advances of pyrotinib in clinical studies are highlighted with very encouraging outcomes in patients with HER2-postive advanced breast cancer.