Discovery of Novel Allosteric EGFR L858R Inhibitors for the Treatment of Non-Small-Cell Lung Cancer

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Addressing resistance to third-generation EGFR TKIs such as osimertinib via the EGFR C797S mutation remains a highly unmet need in EGFR-driven non-small-cell lung cancer (NSCLC). The discovery of novel allosteric inhibitors such as EGFRai-51 and EGFRai-57 to overcome EGFR C797S-mediated resistance in patients harboring the activating EGFR L858R mutation are presented. These allosteric EGFR inhibitors demonstrate robust tumor regression in a mutant EGFR L858R/C797S tumor model. Additionally, EGFRai-57 demonstrates superior efficacy in combination with osimertinib compared to the single agents in an H1975 EGFR L858R/T790M NSCLC xenograft model. These data highlight the potential of using EGFRai-57 as a single agent against EGFR L858R/C797S and EGFR L858R/T790M/C797S and as combination therapy for EGFR L858R- and EGFR L858R/T790M-driven NSCLC.

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