

Synergistic Effects of Combination Therapy With Anti-EGFR and Anti-Src Therapy in Colorectal Cancer

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Background: Cetuximab, a monoclonal antibody to the ligand-binding domain of the epidermal growth factor receptor (EGFR), has demonstrated benefit for patients with metastatic colorectal cancer regardless of their EGFR expression levels. This suggests that other factors may determine sensitivity to this agent. Activation of Src, a non-receptor tyrosine kinase, is a potential mediator of chemoresistance. Increased levels of Src have been correlated with more aggressive phenotypes and poorer prognosis in patients. Combined Src and EGFR inhibition may provide additional benefit.

Methods: We investigated the combination of cetuximab and dasatinib (BMS-354825), a Src inhibitor recently approved by the US Food and Drug Administration (FDA) for chronic myelogenous leukemia. Two cell lines with low and moderate levels of unmutated EGFR were utilized: HT29 and LS174T, respectively. MTT assays were performed after 48 hours of drug exposure. Clonogenic assays were analyzed after 14 days of continuous drug exposure. Formal synergy was determined by CalcuSyn software (Biosoft, Great Shelford, Cambridge, United Kingdom).

Results: Neither LS174T nor HT29 cells are responsive to cetuximab in the MTT assay at clinically relevant doses. The IC₅₀'s for dasatinib in LS174T and HT29 are outside the range that has been achievable in patients. However, the combination of cetuximab and dasatinib showed synergistic growth inhibition at clinically achievable doses in the LS174T cell line, with supra-additivity in the HT29 cell line. This effect was confirmed

in the clonogenic assay with significant augmentation in the inhibition of the clone formation with the combination of agents. Preliminary flow cytometry results suggest that the mechanism is due to an increase in apoptosis. Molecular studies exploring the mechanism of interaction of the EGFR and Src inhibitors are in progress and will be presented.

Conclusions: The combination of dasatinib and cetuximab are synergistic in vitro. Xenograft studies will explore the in vivo relevance of the combination. A phase I trial of 5-fluorouracil (5-FU), oxaliplatin, dasatinib, and cetuximab is planned in metastatic colorectal cancer.