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Clinical responses to ERK inhibition in *BRAF*^{V600E}-mutant colorectal cancer predicted using a computational model

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Approximately 10% of colorectal cancers harbor *BRAF*^{V600E} mutations, which constitutively activate the MAPK signaling pathway. We sought to determine whether ERK inhibitor (GDC-0994)-containing regimens may be of clinical benefit to these patients based on data from in vitro (cell line) and in vivo (cell- and patient-derived xenograft) studies of cetuximab (EGFR), vemurafenib (BRAF), cobimetinib (MEK), and GDC-0994 (ERK) combinations. Preclinical data was used to develop a mechanism-based computational model linking cell surface receptor (EGFR) activation, the MAPK signaling pathway, and tumor growth. Clinical predictions of anti-tumor activity were enabled by the use of tumor response data from three Phase 1 clinical trials testing combinations of EGFR, BRAF, and MEK inhibitors. Simulated responses to GDC-0994 monotherapy (overall response rate = 17%) accurately predicted results from a Phase 1 clinical trial regarding the number of responding patients (2/18) and the distribution of tumor size changes ("waterfall plot"). Prospective simulations were then used to evaluate potential drug combinations and predictive biomarkers for increasing responsiveness to MEK/ERK inhibitors in these patients.

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