Clinical responses to ERK inhibition in BRAFV600E-mutant Colorectal Cancer Predicted Using a QSP-based Computational Model

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Objectives: Approximately 10% of colorectal cancers (CRC) harbor BRAFV600 mutations, driving constitutive activation of the MAPK signaling pathway and a poor prognosis. However, these patients do not respond to BRAF and MEK inhibitor treatments. We sought to determine whether ERK inhibitor (GDC-0994)-containing regimens may be of clinical benefit to these patients.

Methods: A mechanism-based computational model, linking cell surface receptor (EGFR) engagement, the MAPK cascade, feedback mechanisms (i.e. DUSP, SPRY phosphatases) and tumor growth regulation was constructed from literature data. The model consisted of 38 species and 103 parameters, implemented as a system of logic-based and ordinary differential equations in MATLAB SimBiology™. Signal transduction parameters, drug-target IC50 values, and cell proliferation and turnover rates were estimated using data from panels of BRAFV600-CRC cell lines and xenografts treated with EGFR (cetuximab), BRAF (vemurafenib), MEK (cobimetinib), and ERK (GDC-0994) inhibitors.

Predictions of clinical activity (overall response rates; ORR) were enabled by the use of tumor response data from three Phase 1 clinical trials testing combinations of EGFR, BRAF and/or MEK inhibitors.

Results: Simulated responses to GDC-0994 monotherapy in a virtual population of BRAF-V600-mutant tumors (ORR = 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”). Synergistic activity was predicted for the combination with cobimetinib (60 mg, daily), increasing to 30% ORR. Loss of cellular dependence on continued MAPK signaling was predicted as the main driver of resistance. That is, approximately 2/3 BRAFV600E-CRC tumors harbor clones capable of activating other oncogenic pathways, and thus survive and proliferate despite MEK/ERK inhibition.

Conclusions: Increasing response rates to MAPK inhibition in BRAFV600E-CRC will necessitate either the use of predictive biomarkers to pre-select patients with increased MAPK-dependence, or combination with agents targeting orthogonal oncogenic pathways or survival mechanisms.