Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells

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The RAS/RAF/MEK/MAPK and the PTEN/PI3K/AKT/mTOR pathways are key regulators of proliferation and survival in human cancer cells. Selective inhibitors of different transducer molecules in these pathways have been developed as molecular targeted anti-cancer therapies.

The in vitro and in vivo anti-tumor activity of pimasertib, a selective MEK 1/2 inhibitor, alone or in combination with a PI3K inhibitor (PI3Ki), a mTOR inhibitor (everolimus), or with multi-targeted kinase inhibitors (sorafenib andregorafenib), that block also BRAF and CRAF, were tested in a panel of eight human lung and colon cancer cell lines. Following pimasertib treatment, cancer cell lines were classified as pimasertib-sensitive (IC50 for cell growth inhibition of 0.001uM) or pimasertib-resistant. Evaluation of basal gene expression profiles by microarrays identified several genes that were up-regulated in pimasertib-resistant cancer cells and that were involved in both RAS/RAF/MEK/MAPK and PTEN/PI3K/AKT/mTOR pathways. Therefore, a series of combination experiments with pimasertib and either PI3Ki, everolimus, sorafenib or regorafenib were conducted, demonstrating a synergistic effect in cell growth inhibition and induction of apoptosis with sustained blockade in MAPK- and AKT-dependent signaling pathways in pimasertib-resistant human colon carcinoma (HCT15) and lung adenocarcinoma (H1975) cells. Finally, in nude mice bearing established HCT15 and H1975 subcutaneous tumor xenografts, the combined treatment with pimasertib and BEZ235 (a dual PI3K/mTOR inhibitor) or with sorafenib caused significant tumor growth delays and increase in mice survival as compared to single agent treatment.

These results suggest that dual blockade of MAPK and PI3K pathways could overcome intrinsic resistance to MEK inhibition.

References: