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

L.P. Ciuffreda[1], F.A.V. Ferraiolo[1], E. Martinelli[2], T. Troiani[3], F. Morgillo[2], S. Costantino[1], G. Martini[3], F. Ciardiello[2], L. Berrino[1]

[1]Seconda Università di Napoli, Dipartimento di Medicina Sperimentale, Sezione di Farmacologia Via Costantinopoli, 16 - 80138 Napoli
[2]Seconda Università di Napoli, Dipartimento di Internistica Clinica e Sperimentale 'F. Magrassi - A. Lanzara', Via Pansini, 5 - 80131 Napoli
[3]Seconda Università di Napoli, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F.Magrassi - A. Lanzara, Via Pansini, 5 - 80131 Napoli

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 and regorafenib), 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:
1. Ciardiello F et al. EGFR antagonists in cancer treatment. N Engl J Med 2008; 358: 1160-74.
2. Wong KK et al. Targeting the PI3K signaling pathway in cancer. Curr Opin Genet Dev 2010;20:87-90.
3. Ward S et al. Therapeutic potential of phosphoinositide 3-kinase inhibitors. Chem Biol 2003;10:207-13.
4. Yuan TL et al. PI3K pathway alterations in cancer: variations on a theme. Oncogene 2008; 27:5497-510.
5. Castellano E et al. RAS Interaction with PI3K: More Than Just Another Effector Pathway.Genes Cancer 2011; 2:261-74.
6. Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003; 3:11-22.
7. McCubrey JA et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta 2007;17:1263-84.
8. Shaw RJ et al. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature 2006;441:424-30.
9. Cantley LC. The phosphoinositide 3-kinase pathway.Science 2002; 296:1655-57.
10. Yeh TC et al. Biological characterization of ARRY-142886 (AZD6244), a potent, highly selective mitogen-activated protein kinase kinase 1/2 inhibitor. Clin Cancer Res 2007;13:1576-1583.