MEK inhibitor

A MEK inhibitor is a chemical or drug that inhibits the mitogen activated protein kinase enzymes MEK1 and/or MEK2. They can be used to affect the MAPK/ERK pathway which is often overactive in some cancers.

Hence MEK inhibitors have potential for treatment of some cancers, especially BRAF-mutated melanoma, and KRAS/BRAF mutated colorectal cancer.

Trametinib (GSK1120212), FDA-approved to treat BRAF-mutated melanoma. Also studied in combination with BRAF inhibitor dabrafenib to treat BRAF-mutated melanoma.

Cobimetinib or XL518, approved by US FDA in Nov 2015 for use in combination with vemurafenib (Zelboraf(R)), for treatment of advanced melanoma with a BRAF V600E or V600K mutation.

Binimetinib (MEK162), is currently in phase 3 clinical trials for ovarian cancer, BRAF mutant melanoma, and NRAS mutant melanoma.

Selumetinib, had a phase 2 clinical trial for non-small cell lung cancer (NSCLC) which demonstrated an improvement in PFS, and is now in phase III development in KRAS mutation positive NSCLC (SELECT-1, NCT01933932). Other ph 3 clinical trials underway include uveal melanoma (failed), and differentiated thyroid carcinoma. PD-325901, for breast cancer, colon cancer, and melanoma A phase II trial for advanced non-small cell lung cancer “did not meet its primary efficacy end point”.

Treatment with the MEK inhibitor U0126 inhibited the activation by TCF7L2 or EGR1 overexpression. Moreover, overexpression of TCF7L2 or EGR1 accelerated the migration and invasion of Esophageal squamous cell carcinoma cells. A synergistic effect was observed between TCF7L2 and EGR1 in amplifying the induction of LCN2 and enhancing migration and invasion. Taken together, a study of Zhao et al., indicates that TCF7L2 and EGR1 are the KTAPs of LCN2, within a positive “LCN2 → MEK/ERK → LCN2” path, to promote the migration and invasion of ESCC cells. Based on their clinicopathological significance, LCN2 and its two expression regulators TCF7L2 and ERG1 might be therapeutic targets for ESCC [1].

1)
Zhao Y, Xia Q, Liu Y, Bai W, Yao Y, Ding J, Lin L, Xu Z, Cai Z, Wang S, Li E, Xu H, Wu B, Xu L, Du Z. TCF7L2 and EGR1 synergistic activation of transcription of LCN2 via an ERK1/2-dependent pathway in esophageal squamous cell carcinoma cells. Cell Signal. 2018 Dec 14. pii: S0898-6568(18)30309-7. doi: 10.1016/j.cellsig.2018.12.007. [Epub ahead of print] PubMed PMID: 30557604.