Discovery and pharmacological characterization of OMO-1, a potent, highly selective and orally bioavailable MET kinase inhibitor

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Abstract:

Activation of the MET/HGF pathway has been linked to tumour formation, metastasis, angiogenesis and resistance to therapeutic agents. Here we present the pharmacological characterization of OMO-1 (formerly JNJ-38877618), a potent, highly selective, orally bioavailable MET kinase inhibitor with nM binding affinity for wild type, M1250T and Y1235D mutants of MET (1.2, 2.1 and, 21 nM Kd). OMO-1 enzyme inhibitory activity against wt MET was superior to the activity of crizotinib (2 vs. 11.7 nM IC50). OMO-1 displayed nM potency against MET amplification/mutant and SOC therapy resistant models. OMO-1 treatment led to stasis of 4 in-vivo models: MET amplified GTL-16 and SNU5 gastric, U87-MG, HGF autocrine glioblastoma and MET exon 14 skipping mutant Hs746T gastric cancer. Regression of MET amplified EBC-1 SqNSCLC was linked to inhibition of MET kinase activation, with the duration of target shut down exceeding plasma exposure times. Stasis in an EGFR inhibitor-resistant PDX model having MET amplification with OMO-1 monotherapy was superior to MetMab/erlotinib induced reduction in growth rate. Combination treatment of EGFR inhibitor with OMO-1 was well tolerated and improved efficacy. OMO-1 monotherapy was ineffective against NSCLC HCC827 EGFR mutant model whilst combination with erlotinib delayed tumour regrowth. In the acquired EGFR inhibitor resistant model (HCC827-ER1) having MET amplification, OMO-1 and erlotinib both partially inhibited tumour growth, whilst combination induced tumour regression. The potent preclinical activity reported here combined with healthy volunteer safety data (NCT01964872), support the ongoing clinical development of OMO-1 in patients with MET pathway-driven tumours, both in monotherapy and combination settings.