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Anti-tumour activity, pharmacokinetic/pharmacodynamic relationships, and *in vivo* mechanism of action of AZD6244 (ARRY-142886), a potent and specific inhibitor of MEK1/2

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Background: The ERK1/2 MAPK signalling pathway is often constitutively activated in human cancers, a feature usually associated with mutational activation of BRAF or RAS components of the pathway. The kinases MEK1/2, downstream of RAS and BRAF and the only acknowledged activators of ERK1/2, are attractive targets for therapeutic intervention. AZD6244 (ARRY-142886) is a potent, selective inhibitor of MEK1/2 kinases that is un-competitive with ATP and is currently being evaluated preclinically and clinically to determine its anti-tumour effects.

Objective: To determine *in vivo* mechanisms by which AZD6244 inhibits tumour growth in sensitive xenografts, and to correlate these with changes in pharmacokinetic and pharmacodynamic biomarkers.

Results: Chronic dosing with 25mg/kg AZD6244 bid p.o. resulted in complete suppression of growth of Colo-205, >90% inhibition of growth of Calu-6, and 73% suppression of growth of SW-620 xenografts. PC-3 xenografts were not growth inhibited *in vivo* by this dose of AZD6244. Following an acute dose of 25mg/kg AZD6244, significant inhibition of ERK1/2 phosphorylation occurred in Calu-6, SW-620 and Colo-205 xenografts. There was an inverse relationship between pERK in Calu-6 xenografts and free plasma drug concentration; a concentration of ~6ng/ml resulted in 50% inhibition of cytoplasmic pERK, and an AUC of ~4µg·h/ml was sufficient for anti-tumour activity. AZD6244 was able to induce apoptosis in the most responsive xenografts (Calu-6 and Colo-205), and to inhibit proliferation and induce a more differentiated phenotype in SW-620 xenografts.

Conclusion: In these xenograft tumour models, AZD6244 treatment is anti-proliferative, pro-apoptotic, and able to induce differentiation, depending on the tumour type.