The effect of PI3 kinase and mTOR inhibitors on spontaneous tumours in PTEN+/− mice

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The PTEN gene is frequently mutated in human cancer. Cells lacking PTEN possess elevated levels of PtdIns(3,4,5)P(3), which induce activation of the PI3K/Akt/mTOR signalling pathway and stimulate cell proliferation, growth and survival. Heterozygous PTEN+/− mice develop a variety of tumours, and our group and others have demonstrated that genetic disruption of the PI3K/Akt/mTOR pathway markedly protects these animals from developing tumours.

In this study, using MRI techniques, we have evaluated the effect of chemical disruption of signalling pathways in spontaneously pre-formed tumours. We measured different cervical lymphomas developed in mice aged 8-10 months and orally administered vehicle alone or specific inhibitors for PI3K or mTOR for 6 weeks. Our results showed that the inhibitor administration induced a clear reduction in tumour volume from the second week of treatment (first time point analysed), which continued to decrease until the sixth week reaching a maximum reduction of 50%. We also observed increased apoptosis within the treated tumours, and Ki67 reactivity was reduced to below 5% in the neoplastic follicular cell population.

In conclusion, our results demonstrate that the administration of specific PI3K and mTOR inhibitors has a marked effect on reducing the volume of preformed lymphomas. This in vivo data support the role of these drugs as improving disease free survival treatment.