mTOR signalling is frequently activated in myeloma, a malignancy of plasma cells that is incurable in the majority of patients. Preclinical results with rapamycin and analogues showed decreased cell proliferation but clinical data with rapalogs have been disappointing. We show that mTOR and PI3-Kinase signalling is preferentially enhanced in the poor prognosis subgroup of myeloma expressing the t(4;14) translocation. In t(4;14) myeloma cell lines, novel ATP-competitive mTOR inhibitors (mTORi) PP242, WYE354 and KU0063 inhibit both TORC1 (pS6 and p4EBP1) and TORC2 (pAKtS473) outputs. TORC1 inhibition is sustained but there is partial recovery of pAKTS473 at longer time points. Incubation of t(4;14) lines with mTORi inhibits proliferation to 8-32% of control at 72 hours (IC50s 250-500nM). Activity is retained in the presence of bone marrow stromal cells. Importantly, there is induction of cell death in a subset of lines and mTORi can markedly sensitise cells to the cytotoxic effects of dexamethasone, a key anti-myeloma therapeutic. Primary samples from 3 patients with myeloma showed reduced cell survival (22-56% of control). In conclusion, novel mTORi show significant preclinical anti-myeloma activity as single agents and in combination with dexamethasone, with preferential effects in the t(4;14) subgroups. These results should inform the design of clinical trials.