FLT-PET is superior to FDG-PET for very early response prediction in NPM-ALK-positive lymphoma treated with targeted therapy.

The prognosis of relapsed or refractory aggressive lymphoma is poor. The huge variety of currently evolving targeted treatment approaches would benefit from tools for early prediction of response or resistance. We used various ALK-positive anaplastic large cell lymphoma (ALCL) cell lines to evaluate two inhibitors, the HSP90 inhibitor NVP-AUY922, and the mTOR inhibitor everolimus, both of which have shown to interfere with ALK-dependent oncogenic signal transduction. Their therapeutic effect was determined in vitro by MTT assay, [(18)F]fluorodeoxyglucose (FDG)- and [(18)F]fluorothymidine (FLT)-uptake, and by biochemical analysis of ALK-induced signaling. Micro-FDG- and FLT positron emission tomography (PET) imaging studies in immunodeficient mice bearing ALCL xenotransplants were carried out with the cell lines SUDHL-1 and Karpas299 to assess early treatment response to NVP-AUY922 or everolimus in vivo. SUDHL-1 cells showed sensitivity to both inhibitors in vitro. Importantly, we detected a significant reduction of FLT-uptake in SUDHL-1 bearing animals using both inhibitors compared with baseline as early as 5 days after initiation of targeted therapy. Immunostaining showed a decrease in Ki-67 and an increase in cleaved caspase-3 staining. In contrast, FDG-uptake did not
significantly decrease at early time points. Karpas299 xenotransplants, which are resistant to NVP-AUY922 and sensitive to everolimus treatment, showed an increase of mean FLT-uptake on day 2 after administration of NVP-AUY299, but a significant reduction in FLT-uptake upon everolimus treatment. In conclusion, we show that FLT-PET but not FDG-PET is able to predict response to treatment with specific inhibitors very early in the course of treatment and thus enables early prediction of treatment efficacy.