

## K7

### **FDG uptake is a surrogate marker for defining the optimal biological dose of the mTOR inhibitor everolimus *in vivo***

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### **Background**

Despite intensive research, optimal biological dosing of mammalian targets of rapamycin (mTOR) inhibitors remains difficult. 2'-deoxy-2'-[<sup>18</sup>F]fluoro-*D*-glucose positron emission tomography (FDG-PET) can detect changes in tumor metabolism early after treatment with anti-cancer drugs. The aim of the study was to test whether FDG-PET can be used to define the optimal biological dose (OBD) of mTOR inhibitors *in vivo*.

### **Methods**

Gastric cancer xenografts were established in nude mice. FDG uptake of tumors was measured at different time points after administration of 0.05, 0.5, 5 and 15 mg/kg of everolimus using a small animal PET system. Tumor volumes were determined by manual caliper measurements. Everolimus blood levels were measured and tumor lysates were analyzed for phosphorylation status of S6 protein by Western blotting. Proliferation of tumor cells was assessed by immunohistochemical staining of Ki-67 antigen.

### **Results**

Everolimus blood levels increased with dose and were highest in the 15 mg/kg group, but the anti-tumor activity of everolimus reached a plateau at a dose of 5 mg/kg, which was defined as the OBD. Correspondingly, FDG uptake of tumors decreased dose-dependently up to a dose of 5 mg/kg. However, FDG uptake in the 5 mg/kg and 15 mg/kg group was similar. Furthermore, everolimus showed a dose-dependent decrease in S6 protein phosphorylation status, and changes in tumor cell proliferation reflected tumor volume and FDG-uptake.

### **Conclusions**

The OBD of everolimus can be determined using FDG-PET *in vivo*. FDG-PET might facilitate dose-finding studies for mTOR inhibitors in clinical trials.