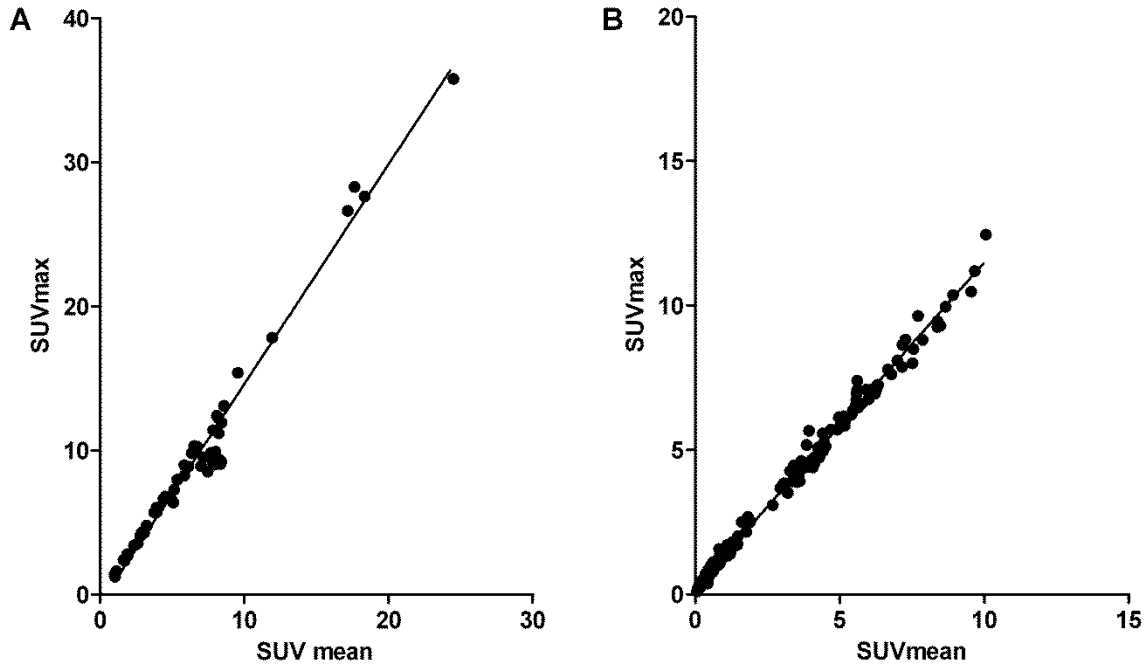
Case Reports

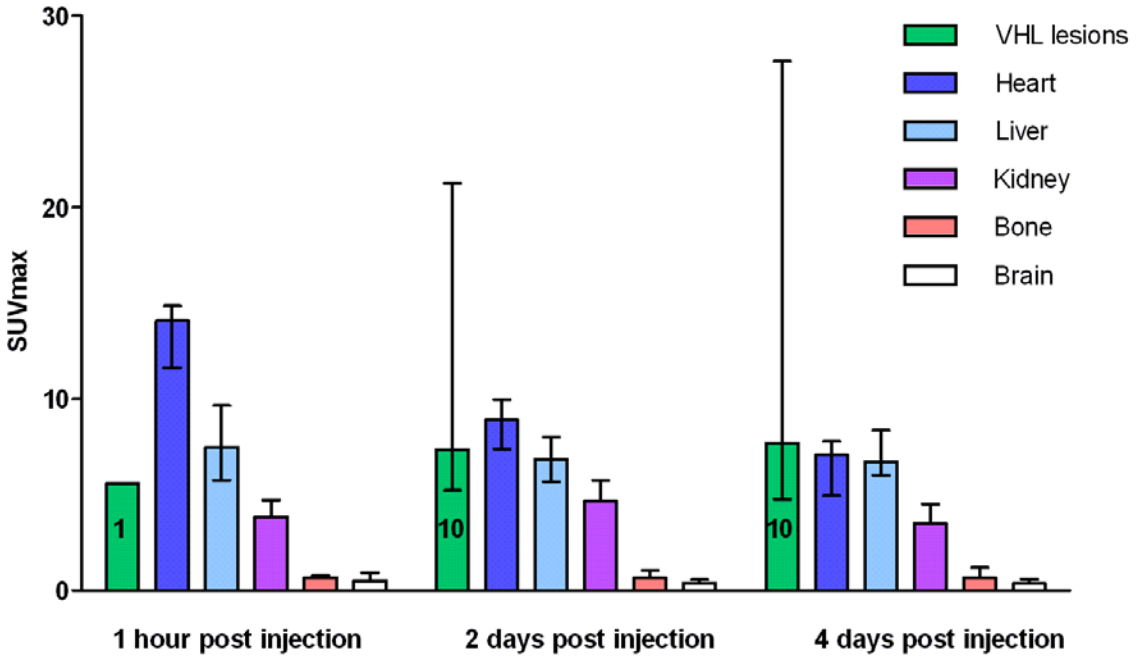
Patient A, a 48-year-old female patient with a c.500G>A mutation, had at trial entry a history of resected bilateral pheochromocytoma, treatment of retinal angioma, a resected cerebellar hemangioblastoma, a partial left nephrectomy for renal cell carcinoma and four progressive solid lesions growing from the left kidney remnant. Baseline MRI scans showed 14 Von Hipple-Lindau disease manifestations (of which five ≥ 10 mm): nine CNS lesions, four solid lesions in the left kidney and opne solid pancreatic mass. Of these, only one cerebellar hemangioblastoma < 5 mm with a SUV_{max} of 1.6 was visible on ^{89}Zr-bevacizumab PET. The PET scan also demonstrated a hot spot in the right kidney, but on MRI no substrate was found (Supplemental Video 1). The PET scan did not show focally increased uptake in recurrent renal cell carcinoma lesions from the left kidney remnant. Four weeks after the PET scan, a radical left tumor nephrectomy was performed including a partial colon resection because of tumor infiltration. Six months later she presented with extensive local recurrence, ascites and liver metastases. She started standard treatment with bevacizumab 10 mg/kg intravenously every 2 weeks plus interferon-α three times per week subcutaneously at a starting dose of 3 million units with the aim to increase the dose to 9 million units three times per week if tolerated. The patient died 2 months later of progressive renal cell carcinoma.

Patient B, a 61-year-old female patient with also a c.500G>A mutation, entered the trial with a history of bilateral retinal angiomas, five craniotomies for resection of hemangioblastomas, embolisation of a cervical spine hemangioblastoma, a radical left nephrectomy for renal cell carcinoma, a partial right nephrectomy and radiofrequency ablation for recurrent renal cell carcinoma. She suffered from ataxia, disturbed balance and diplopia. Baseline MRI scans revealed 13 CNS lesions (eight intracranial, two cervical, two thoracic and one optic nerve localization),

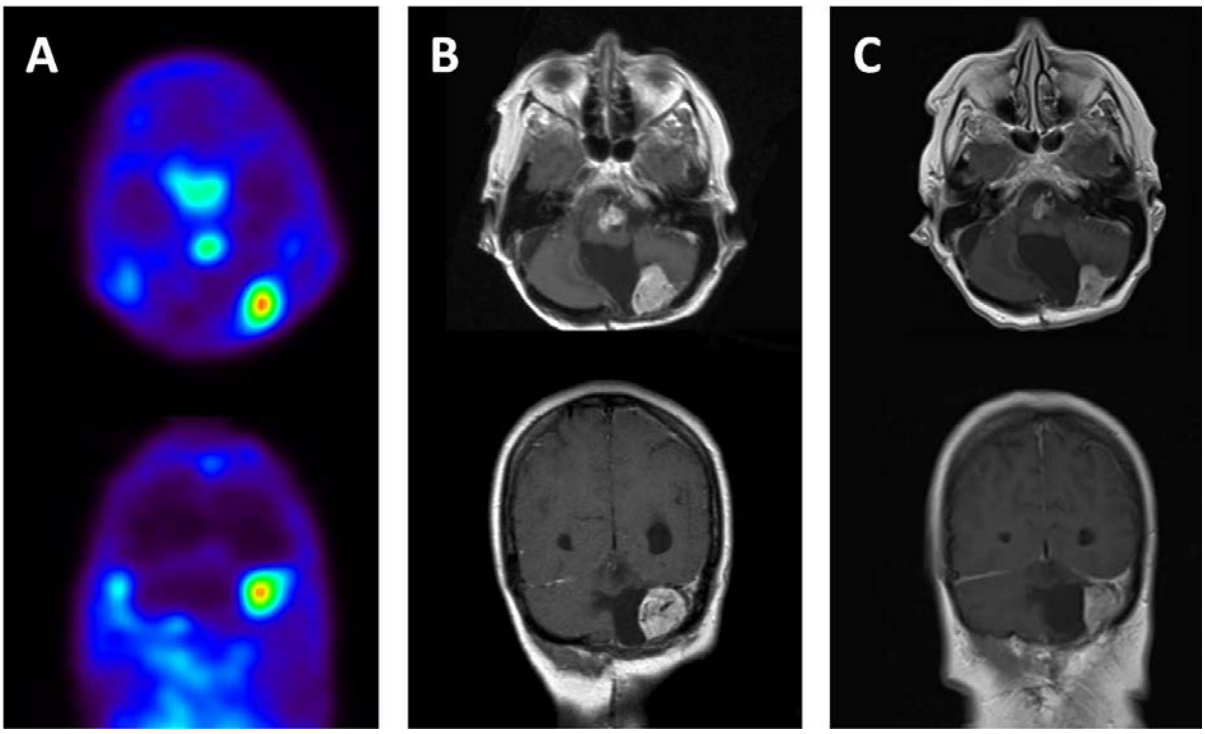
three solid kidney lesions, and one pancreatic lesion suspect for a pancreatic neuroendocrine tumor. Nine lesions were ≥ 10 mm, eight lesions were visible on PET, with a median SUV_{max} of 7.5 (range 2.4 – 28.3) including five CNS lesions (Supplemental Video 2). Five months after the ^{89}Zr-bevacizumab PET scan, her condition deteriorated with dysartria and dysphagia and severe neuropathic pain in the neck, shoulders and arms. Progression of hemangioblastomas in the cerebellum, brain stem and cervical spine was demonstrated on MRI. Surgical or endovascular treatment was not possible, radiosurgery was deemed too dangerous because of the risk of transient increase in vascular permeability and edema. The patient received treatment with bevacizumab plus interferon-α according to the standard regimen for renal cell carcinoma. Two weeks after the first bevacizumab dose, neuropathic pain had resolved completely. Interferon-α was stopped after 8 weeks because of anorexia. Walking and speech improved a little over months. The MRI scan after 3 months of treatment showed a decrease in size of the hemangioblastomas in cerebellum and brain stem (Supplemental Fig. 3) and of the kidney mass, whereas other lesions were unchanged. After 8 months of treatment she developed hydrocephalus because of growth of a cystic component of the cerebellar hemangioblastoma. An endoscopic third ventriculostomy was performed and bevacizumab was continued. After 32 months of bevacizumab treatment with ongoing clinical benefit, her general condition gradually declined although radiologically she continued to have stable disease. Bevacizumab was discontinued after 35 months of treatment and the patient died 2 months thereafter.



Supplemental Figure 1 Correlation between SUV_{mean} and SUV_{max} for Von Hippel-Lindau disease manifestations (A) and normal organs (B).



Supplemental Figure 2 Maximum standardized uptake value (median SUV_{max} with range) of Von Hippel-Lindau disease associated lesions and normal organs on serial PET scans of three patients 1 hour, 2 days and 4 days after ^{89}Zr-bevacizumab injection.



Supplemental Figure 3 PET scan (A) and MRI scans of patient B demonstrating hemangioblastomas in the cerebellum and brain stem before (B) and after 3 months of bevacizumab treatment (C).

Supplemental Table 1 **Treatment in 22 patients during the 12 months following ^{89}Zr-bevacizumab PET**

Patient	Sex	Age	Progressive lesions	Action
1	Male	57	Symptomatic hemangioblastoma	Craniotomy, resection
2	Female	23	None	Surveillance
3	Male	31	Symptomatic hemangioblastoma	Laminectomy, resection
4	Male	61	Symptomatic hemangioblastoma	Craniotomy, resection
5†	Female	61	Multiple symptomatic inoperable hemangioblastomas	Bevacizumab/interferon-α
6	Male	62	2 new asymptomatic hemangioblastomas	Surveillance
7	Female	36	3 new asymptomatic hemangioblastomas	Surveillance
8	Female	29	Symptomatic hemangioblastoma	Craniotomy, resection
9	Male	33	None	Surveillance
10†	Female	48	Recurrent multifocal renal cell carcinoma	Resection
			Metastatic renal cell carcinoma	Bevacizumab/interferon-α
11	Female	29	Growing asymptomatic hemangioblastoma	Surveillance
12	Female	38	None	Surveillance
13	Male	63	1 new asymptomatic hemangioblastoma	Surveillance

14	Female	46	None	Surveillance
15	Female	60	Metastatic pancreatic neuro-endocrine tumor, progression not assessed	Everolimus
16	Male	26	Growing asymptomatic hemangioblastoma	Surveillance
17	Male	32	None	Surveillance
18	Male	31	1 new asymptomatic hemangioblastoma	Surveillance
19	Male	50	None	Surveillance
20	Male	46	Symptomatic hemangioblastoma	Laminectomy, resection
21	Male	66	None	Surveillance
22	Male	35	None	Surveillance

† = Detailed case report in supplemental material.