



Alpha- vs. beta-targeted radiotherapy in a GRP-receptor positive mouse xenograft model, efficacy and toxicity

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Why gastrin releasing peptide receptor targeting

tissue	GRP-R incidence	GRP-R density (dpm/mg tissue)	potential clinical application
high-grade PIN prostate cancer bone metastasis (androgen independent)	26/26* 30/30* 4/7*	4351 ± 649* 5241 ± 927* 3863 ± 2018*	PET/CT: TNM-staging, restaging therapy: recurrent disease, M+, mainly androgen independent
breast cancer lymphnode metastases	50/68+ 10/15+	9819 ± 530+ 8206 ± 6250+	PET/CT: TNM-staging, restaging therapy: M+
GIST distant metastases	10/15† 4/4†	9420 ± 10945† 7824 ± 7522†	PET/CT: TNM-staging, restaging Imatinib (Glivec®) resistant GIST
for comparison	sst ₂ -R incidence	sst ₂ -R density (dpm/mg tissue)	
Ileal carcinoids	26/27‡	5433 ± 3918‡	Octreoscan: primary diagnostics, staging therapy: ¹⁷⁷ Lu-DOTATATE or ⁹⁰ Y-DOTATOC

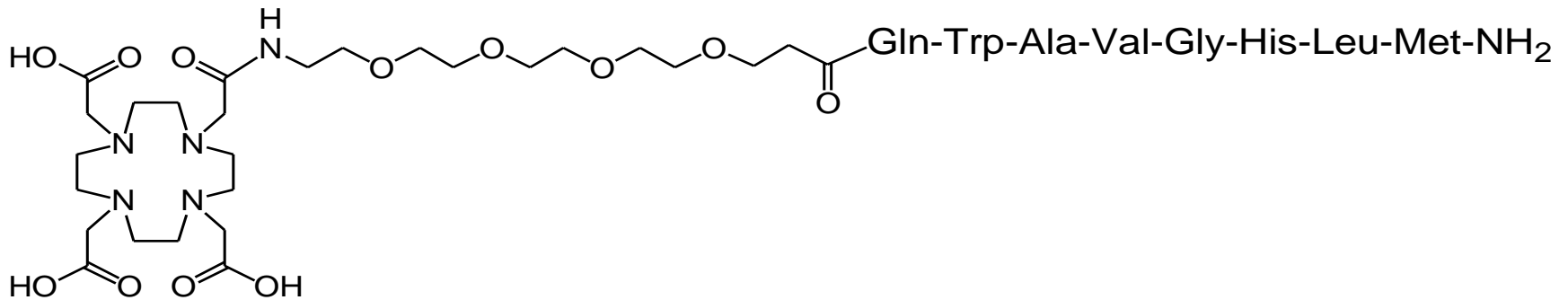
* Markwalder R, Reubi JC, Cancer research 59:1152-1159, 1999

+ Reubi JC, Gugger M, Waser B, Eur J Nucl Med 29:855-862, 2002

† Reubi JC, Körner M, Waser B et al., Eur J Nucl Med Mol Imaging 31:803-810, 2004

‡ Reubi JC, Waser B, Eur J Nucl Med Mol Imaging 30:781-793, 2003

The GRP receptor analogue DOTA-PESIN



The DOTA chelator can be labelled with different radionuclides:

For diagnostic applications:

¹¹¹ In	SPECT/CT
⁶⁸ Ga	PET/CT

For therapeutic applications:

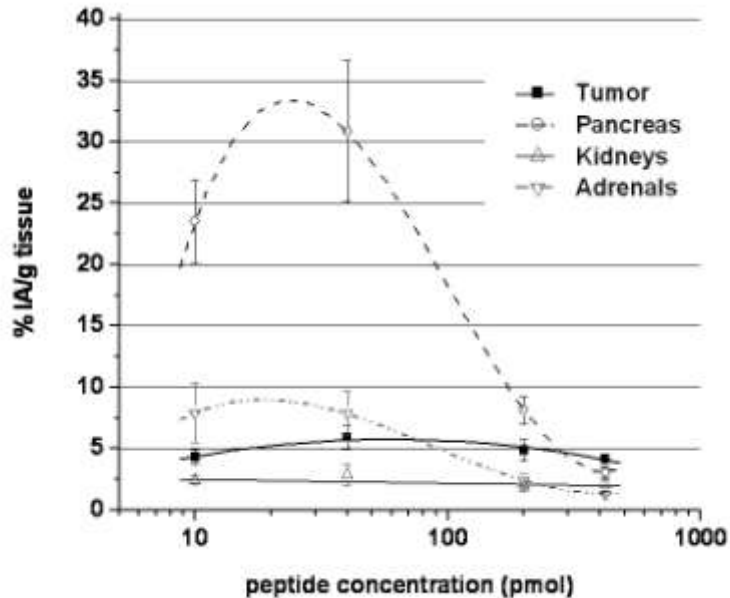
	rays	energy	half-life	maximal range
⁹⁰ Y	β ray	2.28 MeV (100%)	64.1 h	11 mm
¹⁷⁷ Lu	β ray	0.497 MeV (79%)	159 h	1.6 mm
²¹³ Bi	α ray	8.4 MeV (98%)	0.8 h	0.00008 mm

Methods

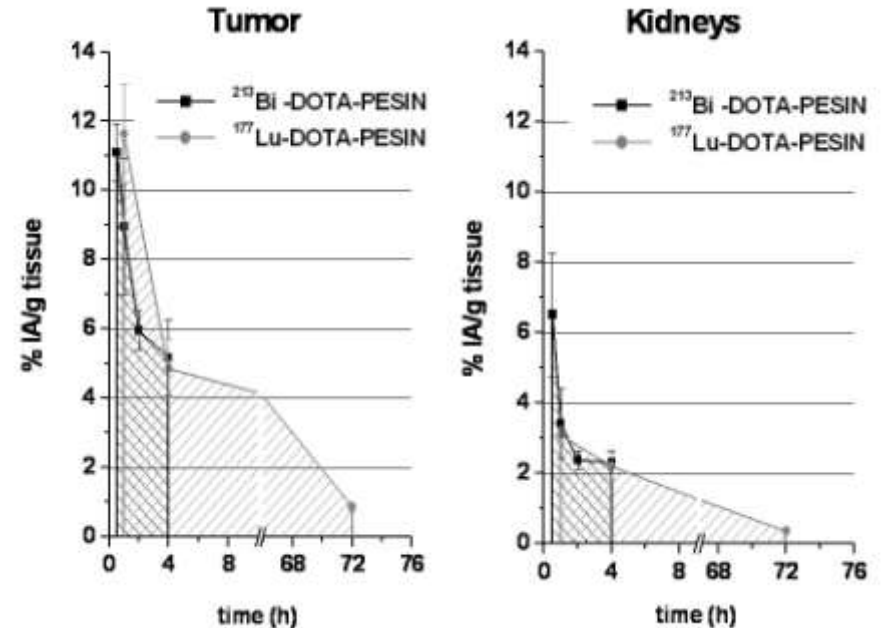
- Biodistribution with different peptide concentrations at different time points was carried out in human prostate cancer xenograft (PC-3) bearing nude mice in order to estimate the mean absorbed dose.
- The impact of ^{213}Bi -DOTA-PESIN treatment on the GRP-R level was studied.
- After injection of 5 – 45 MBq ^{213}Bi -DOTA-PESIN or 30 – 120 MBq ^{177}Lu -DOTA-PESIN survival and maximal tolerated dose (MTD) were assessed.
- Histological investigations were carried out on different organs of non tumor bearing nude mice 5 months after ^{213}Bi -DOTA-PESIN and ^{177}Lu -DOTA-PESIN treatment.

Results: Biodistribution in PC-3 tumor bearing nude mice

Peptide concentration dependent biodistribution
4h after iv. injection of ^{177}Lu -DOTA-PESIN



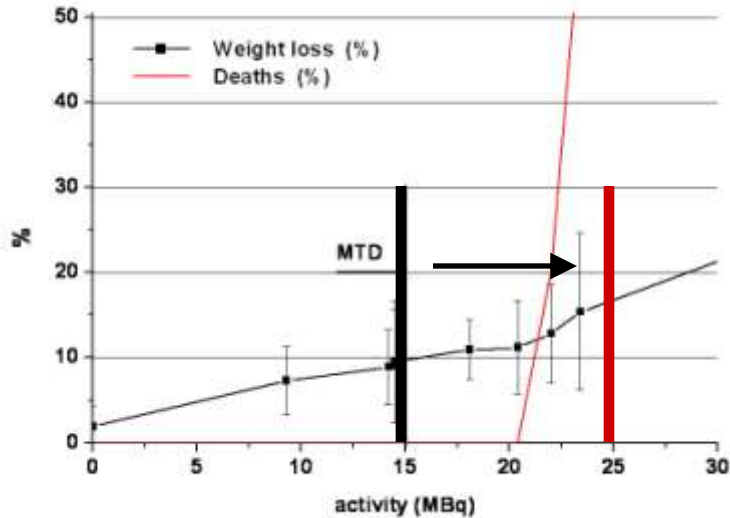
Comparison of **200pmol** ^{213}Bi -/ ^{177}Lu -DOTA-PESIN
biodistribution in PC-3 tumor bearing mice



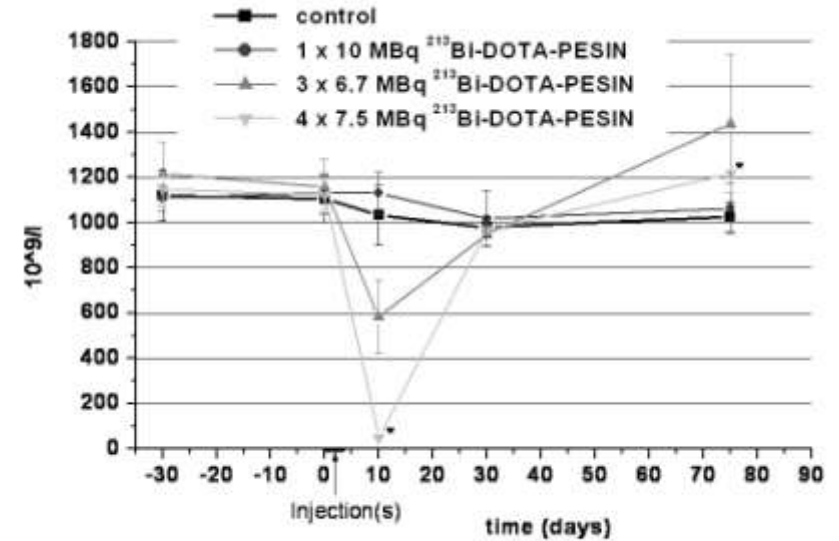
	^{213}Bi -DOTA-PESIN	T-test	^{177}Lu -DOTA-PESIN
tumor uptake 1h p.i.	9.0 2.0%IA/g	ns	11.6 1.4%IA/g
kidney uptake 1h p.i.	3.4 1.0%IA/g	ns	3.1 0.4%IA/g
tumor-to-kidney ratio 1h p.i.	2.2		2.9

Results: MTD and hematotoxicity of ^{213}Bi -DOTA-PESIN

Maximal tolerated dose (MTD) of ^{213}Bi -DOTA-PESIN



Platelet count in nude mice after ^{213}Bi -DOTA-PESIN treatment



* only one animal survived

Injection protocol for ^{213}Bi -DOTA-PESIN treatment:

1h tumor uptake
9.0 2.0 %IA/g

1h tumor uptake
7.3 2.0 %IA/g ns

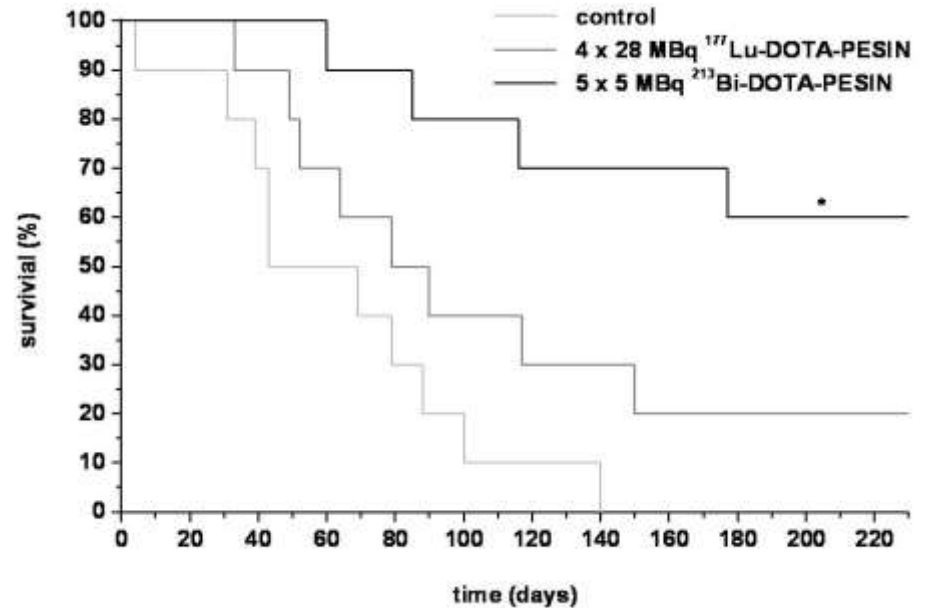
1h tumor uptake
7.1 1.1 %IA/g ns

Autoradiography:
+ no GRP-R down regulation



Results: Therapeutic efficiency of ^{177}Lu - vs. ^{213}Bi -DOTA-PESIN

* ^{213}Bi -DOTA-PESIN treatment (25MBq = MTD) significantly increased life span over that of ^{177}Lu -DOTA-PESIN treatment (112MBq = MTD). (p = 0.043)

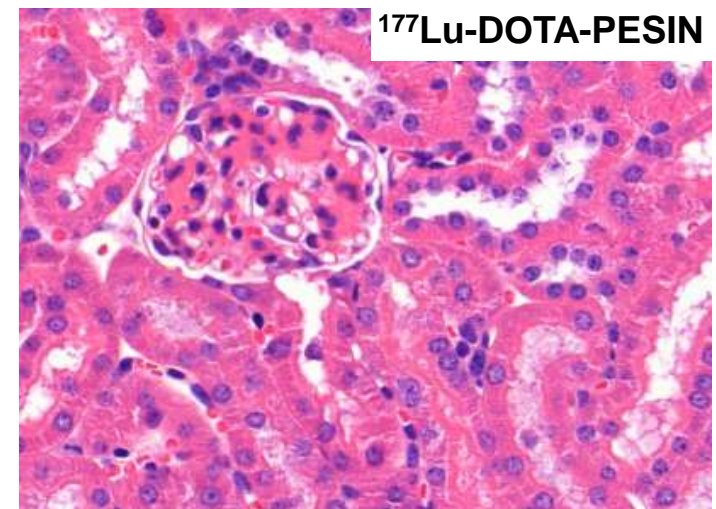
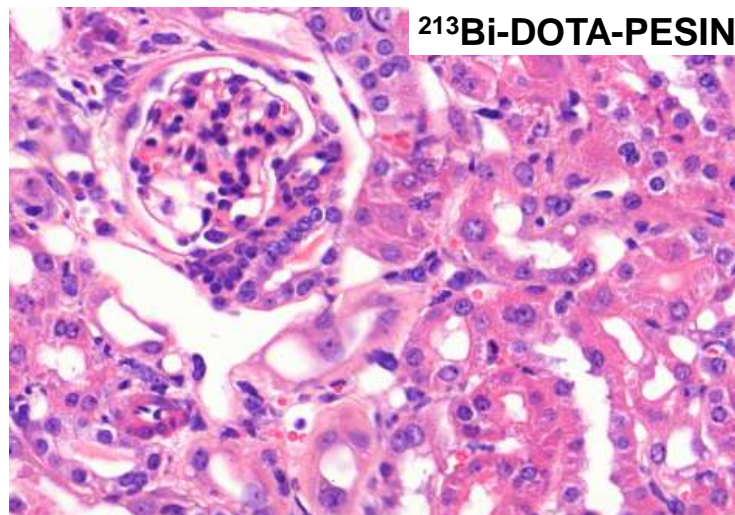


	^{213}Bi -DOTA-PESIN (n = 10)	^{177}Lu -DOTA-PESIN (n = 10)
injected activity = MTD	5 x 5 MBq = 25 MBq	4 x 28 MBq = 112 MBq
dose deposition in the tumor	0.52 Gy/MBq = 13 Gy	0.17 Gy/MBq = 19 Gy
dose deposition in the kidneys	0.24 Gy/MBq = 6 Gy	0.06 Gy/MBq = 6.7 Gy
complete remission (WHO)	70%	20%
partial response (WHO)	30%	10%
progressive disease (WHO)	0%	70%

Results: Organ and kidney toxicity 5 months post injection

	²¹³ Bi-DOTA-PESIN (n = 20)	¹⁷⁷ Lu-DOTA-PESIN (n = 20)
injected activity = MTD	5 x 5 MBq = 25 MBq	4 x 28 MBq = 112 MBq
organ toxicity: pancreas, adrenals	none	none
kidney toxicity: - glomerulopathy - tubular degeneration - infarction severe kidney toxicity (grade 4 and 5)	none grade 2 – 4 (reversible) grade 0 – 5 (progressive) 25%	grade 0 – 2 (progressive) none none 0%

*microscopic findings 3 months after injection – finding levels: grade 1: minimal, grade 2: slight, grade 3: moderate, grade 4: marked, grade 5: massive



Conclusion

High specific tumor uptake of ^{213}Bi -DOTA-PESIN enables high dose deposition of an alpha-emitting radionuclide in the PC-3 tumor.

In addition, ^{213}Bi labeled DOTA-PESIN is significantly more efficient than ^{177}Lu -DOTA-PESIN but shows a higher risk of kidney toxicity.

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Thank you for your attention