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^{177}Lu-3BP-227 for neurotensin receptor 1-targeted therapy of metastatic pancreatic adenocarcinoma – first clinical results

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ABSTRACT

Objective: Neurotensin receptor 1 (NTR1) is overexpressed in ductal pancreatic adenocarcinoma, which is still one of the deadliest cancers with a very poor prognosis. Eligible patients were offered radiopharmaceutical treatment with the novel NTR1 antagonist ^{177}Lu-3BP-227 as salvage therapy.

Methods: Six patients with confirmed ductal pancreatic adenocarcinoma who had exhausted all other treatment options received ^{177}Lu-3BP-227 for evaluation of NTR1 expression *in vivo*. Three patients received treatment activities between 5.1 and 7.5 GBq.

Results: Administration of ^{177}Lu-3BP-227 was well tolerated by all patients. Kidneys were identified as the dose-limiting organ. The most severe adverse event was reversible grade 2 anemia. One patient achieved a partial response and experienced significant improvement of symptoms and quality of life. This patient survived 13 months from diagnosis and 11 months from start of ^{177}Lu-3BP-227 therapy.

Conclusion: This initial report provides first clinical evidence of the feasibility of treatment of ductal pancreatic adenocarcinoma using ^{177}Lu-3BP-227.

INTRODUCTION

Pancreatic adenocarcinoma has an extremely poor prognosis. Mortality virtually equals incidence, and the five year survival rate of metastatic pancreatic adenocarcinoma is less than 5% (*1*). In particular, patients with new onset ascites have a life expectancy of approximately two months only, and death typically occurs by inanition rather than due to large tumor burden. At the time of diagnosis, most patients are ineligible for surgery due to metastatic spread or local tumor invasion (*2*). For metastatic disease, current treatment options are limited to cytotoxic chemotherapy (*1*).

NTR1 is highly expressed in ductal pancreatic adenocarcinoma, but not in normal pancreatic tissue or chronic pancreatitis (*3*). Furthermore, it has been shown that incidence of NTR1 expression and receptor density increases with higher malignancy of the pancreatic lesion, and that hepatic metastases express NTR1 in similar intensity as the primary tumor (*4*). The very restricted expression in normal tissues, which is limited to the central nervous system and the intestinal tract (*5*), make NTR1 a promising compound for targeted radioligand therapy (TRLT) of ductal pancreatic adenocarcinoma.

3BP-227 is a DOTA-conjugated NTR1 antagonist that has been developed based on the previously described SR142948A (*6*). In a preclinical animal model, ^{177}Lu-labeled 3BP-227 significantly inhibited tumor growth in the NTR1-positive HT29 xenograft model and resulted in a nine-fold increase in tumor doubling time as well as a tumor growth delay of more than 5 weeks (*7*).

Here we report our initial experience with TRLT using ^{177}Lu-3BP-227 in patients with metastatic pancreatic adenocarcinoma after exhaustion of all other treatment options.

MATERIALS AND METHODS

Patients and Regulatory Issues

^{177}Lu-3BP-227 was administered to six pancreatic adenocarcinoma patients and offered as salvage therapy (if the patient's condition allowed doing so) in accordance with paragraph 37 of the updated Declaration of Helsinki, "Unproven Interventions in Clinical Practice", and in accordance in accordance with the German Medical Products Act AMG §13 2b.). Each therapy was approved individually by a certified institutional tumor board. Since this is a retrospective report on findings of regular clinical care and not a systematic clinical trial, additional approval by an ethics committee was waived. All patients signed a detailed written informed consent for the treatment, as well as for the use of their anonymized clinical data for scientific purposes. The institutional review board (IRB or equivalent) approved this study and all subjects signed a written informed consent. Patient characteristics are given in Table 1.

Radiopharmaceuticals

GMP-grade 3BP-227 was manufactured by Soneas Research Ltd. (Budapest, Hungary). 25 µg (22.1 nmol) of 3BP-227 per 1 GBq ^{177}Lu (non-carrier added, ITG, Germany) were dissolved in 0.4 mL buffer (0.4 M acetate, 0.325 M gentisic acid, pH 5.5). 3BP-227 dissolved in buffer was mixed with ^{177}Lu and heated to 85°C for 30 min. The compound/radioactivity ratio was chosen to yield a specific activity of the final preparation of approx. 45 MBq/nmol, which is routinely achieved with DOTA-conjugated compounds and clinically accepted (*8,9*)

Quality control was performed using thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). For HPLC analysis, the labeling solution was analyzed with an Aeris PEPTIDE 3.6 µm XB-C18; 100 x 4.6 mm (Phenomenex). Solvent A: MeCN, 0.1% TFA, solvent B: H2O, 0.1% TFA; gradient: 100% B to 100% A within 20 min, flow rate 0.8 ml/min; detector: NaI (Raytest), DAD 254 nm. Retention time of the labeled product: 9.9 min. For TLC analysis, 2 µl of the labeling solution were analyzed using an ITLC SA system (Varian, 10 x 1 cm) in citrate buffer (0.1 M, pH 5) and Raytest Minigita. Radiochemical yield: ≥ 95%, radiochemical purity: ≥ 95%.

Formulation for Intravenous Injection

If the HPLC result conformed to the specifications (radiochemical yield: ≥ 95%, radiochemical purity: ≥ 95%), the reaction mixture was diluted with 0.9% NaCl solution to a volume of 2 ml. After retrieval of reference samples and samples for sterility testing, 0.9% NaCl solution was added to a final volume of 10

ml using a µ DDS-A unit (TEMA Sinergie). This step included sterile filtration and dispensing into a shielded syringe.

Sterility and Pyrogen Tests

The LAL test for pyrogen concentration was performed on-site using the non-radioactive solution of 3BP-227 in 0.4 M sodium acetate buffer. The result was available before administration of ^{177}Lu-3BP-227. Sterility of the radiolabeled product was determined according to Eur Ph 2.6.1 on-site at the Zentralklinik Bad Berka. All master batches during set-up of the radiolabeling procedure were tested for sterility; thus, it was established that the product of the radiolabeling procedure generally conforms to sterility specifications (no growth). Test results of individual batches became available after administration.

Scintigraphy and SPECT/CT Imaging

The kinetics of ^{177}Lu-3BP-227 were determined on the basis of five planar whole-body scintigraphies in defined time order after administration of the radiopharmaceutical (p.i.). The scans for dosimetry studies were acquired from immediately after infusion and up to 119 hours p.i. using a MEDISO spirit DH-V dual-headed gamma camera, MeGP collimator, 15% energy window, peak at 208 keV, speed 15 cm/min. Scintigrams were analyzed by the use of regions of interest (ROI). After geometric mean and background correction, time-dependent time–activity curves were obtained and fitted to mono- or biexponential functions (software ORIGIN PRO 8.1G).

Dosimetry Calculations

The dosimetric approach was based on the Medical Internal Radiation Dose scheme. The residence time and cumulated activity as well as the uptake and effective half-life were then calculated, and the mean absorbed doses were estimated by using the OLINDA/EXM software. Uptake values were calculated as fraction of administered activity (%IA), and effective half-lives, residence times, and mean absorbed organ and tumor doses were obtained for whole body, normal tissues and organs as well as tumor lesions that were large enough and sufficiently distinguishable from the surrounding tissue to allow the definition of a ROI. For lesions that were too small to allow clear demarcation, dosimetry calculations were not performed. The ROIs for normal tissue and background were placed over those regions showing no tumor involvement.

Treatment Procedure

To prevent nausea and emesis, 8 mg Ondansetron and 8 mg Dexamethasone were injected before therapy. ^{177}Lu-3BP-227 was administered intravenously over 10–15 min using a dedicated infusion

system. Intraperitoneal administration of ^{177}Lu-3BP-227 was performed under ultrasound guidance. Dexamethasone (4 mg) was given orally for 3 consecutive days following ^{177}Lu-3BP-227 therapy.

The administered activity was individually chosen based on uptake in the tumor lesions after infusion of 1.2 - 1.5 GBq of ^{177}Lu-3BP-227, thus applying a similar scheme as used by Wild et al. for the evaluation of ^{177}Lu-DOTA-JR11 (*10*). Treatment planning was performed based on the clinical condition of the patient, hematological and renal function, as well the practical guidance on peptide receptor radionuclide therapy (*8*).

All patients received ^{177}Lu-3BP-227 intravenously. However, patient 3 received the second, third, and fourth TRLT intraperitoneally due to the presence of extensive peritoneal carcinomatosis (*11,12*).

Clinical, Radiological, and Laboratory Follow-up

The records of the patients were reviewed for any incidence of hematological, gastrointestinal, and other adverse events. Circumstances that resulted in cessation or delay in treatment were documented. Alterations in carbohydrate antigen 19-9 (CA 19-9) serum levels were also evaluated.

A systematic follow-up was performed in all patients by the determination of the relevant laboratory parameters every 2 weeks after therapy by the referring physicians/oncologists. If the patient's general condition allowed, an FDG PET/CT imaging was performed 8-12 weeks after therapy and was used to determine treatment efficacy.

RESULTS

Patient 1 and 2

Patient 1 and 2 presented with very advanced pancreatic adenocarcinoma with extensive metastases. Patient 1 had unresectable disease (see Supplementary Figure 1 for ^{18}FDG-PET scan) and categorically refused chemotherapy. Patient 2 had a treatment history of 56 months with several different chemotherapeutic regimens including oxaliplatin, gemcitabine, FOLFIRI (folinic acid/fluorouracil/irinotecan), and nab-paclitaxel. Both patients received an intravenous application of 1.2 GBq of ^{177}Lu-3BP-227 (patient 1) and 1.5 GBq (patient 2), respectively, which was tolerated without any side effects. In both patients there was excellent uptake of ^{177}Lu-3BP-227 in the primary tumors and metastases (Fig. 1, Table 2). However, death occurring within two weeks from dosimetry (patient 1) and the identification of a previously unknown brain metastasis (patient 2) prevented further treatment and follow-up.

Patient 3

Seven months after experiencing back pain, diarrhea and weight loss, this 59 year-old female patient was diagnosed with ductal adenocarcinoma of the pancreatic body. Hepatic, pulmonary, and lymph node metastases were present at the time of diagnosis as well as infiltration of the visceral blood vessels and peritoneal carcinomatosis with massive ascites production. Additional medical conditions included severe cachexia due to malnutrition (hypoalbuminemia, hypoproteinemia), a non-functioning left kidney and diabetes mellitus. Following diagnosis, the patient received palliative chemotherapy (FOLFIRINOX: folinic acid/fluorouracil/irinotecan/oxaliplatin and FOLFOX: folinic acid/fluorouracil/oxaliplatin), but presented with progressive disease after initiation of chemotherapy during the scheduled restaging, and had thus exhausted all conventional treatment options with an extremely poor prognosis.

After an initial intravenous application of 1.5 GBq of ^{177}Lu-3BP-227 to assess tumor uptake and organ dosimetry, the patient first received two further cycles (four weeks) of FOLFOX, and then started a series of three intraperitoneal administrations of 6.4 GBq, 7.5 GBq, and 5.5 GBq, respectively, at intervals of 8 to 10 weeks (Supplementary Table 1). The application of ^{177}Lu-3BP-227 was tolerated without any side effects (e.g., no nausea or vomiting) and without significant changes in pulse and blood pressure. SPECT/CT imaging 96 hours after the application demonstrated uptake in the primary tumor in the pancreas body and diffuse accumulation in the peritoneal carcinomatosis (Fig. 2). Dosimetry calculations

identified the single functioning kidney as the dose limiting organ (Table 2). The administered cumulative activity of 20.8 GBq delivered a total dose of 22 Gy to the kidney. Serum creatinine levels and glomerular filtration rate remained normal during the treatment and follow-up (Supplementary Table 2).

At baseline, the patient presented with a functional status of <70% according to the Karnofsky performance scale, grade 1 anemia (hemoglobin 6.6 mmol/l), grade 1 thrombocytopenia (platelets 125 Gpt/l), and strongly increased serum CA 19-9 (2555 U/mL). During treatment, there was thrombocytopenia between grade 0 and 1 with recovery between administrations and temporary grade 1 leukopenia (Fig. 3 A-C, Supplementary Table 1). There was a short and reversible episode of grade 2 anemia before the last treatment. CA 19-9 levels decreased during treatment from 2555 to 220 U/ml and remained at this level during follow-up (Fig. 3 D).

The size and metabolic activity of the pancreatic primary tumor decreased significantly during ^{177}Lu-3BP-227 treatment as shown by FDG-PET (Fig. 4). Metabolic activity of supra- and retroclavicular lymph nodes as well as pulmonary metastases also decreased, and liver metastases were not detectable anymore. According to Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) and Response Evaluation Criteria in Solid Tumors (RECIST), the patient achieved a partial remission of the disease. Ascites production decreased allowing drainage to be reduced from twice daily to twice weekly. The general status and quality of life of the patient improved considerably during treatment. The patient lived for 11 months from the start of ^{177}Lu-3BP-227 treatment (13 months from diagnosis, when ascites was already present). The patient reported significant improvement in her quality of life during this period. However, death occurred following bacteremia and septic shock as a complication of central venous catheter placement.

Patients 4 – 6

In patient 4, no uptake was detected in the tumor lesions after the intravenous application of 1.5 GBq ^{177}Lu-3BP-227, and therefore, therapy was not indicated.

The pancreatic primary tumors of patients 5 and 6 had been surgically removed, and both patients had received several cycles of chemotherapy with gemcitabine and FOLFIRINOX. Nevertheless, both patients presented with progressive disease. Intravenous application of 1.5 GBq ^{177}Lu-3BP-227 showed substantial uptake in the tumor lesions, and patients 5 and 6 received TRLT with 5.5 and 5.1 GBq ^{177}Lu-3BP-227, respectively. Both patients tolerated the therapy without any side effects, and no adverse events

occurred during the immediate follow-up. However, both patients died within weeks due to rapid disease progression.

Dosimetry and Adverse Events

Dosimetry identified the kidneys as dose-limiting organ in all patients. The absorbed organ doses ranged from 0.7 to 1.4 mSv/MBq. The dose to bone marrow, liver and gastrointestinal tract was consistently low (Table 2). Whole body planar images of all patients are shown in Supplementary Figure 2 and detailed pharmacokinetic data of the patients who underwent dosimetry are shown in Supplementary Figure 3.

All patients presented with grade 1 anemia and 2 patients (P3, P4) also had grade 1 thrombocytopenia before commencing treatment with ^{177}Lu-3BP-227. The administration of ^{177}Lu-3BP-227 was tolerated without any acute side effects by all patients. The most severe adverse event that was considered to be potentially related to ^{177}Lu-3BP-227 treatment was reversible grade 2 anemia (P3). A detailed account of adverse events and laboratory follow up is presented in Supplementary Tables 1 - 3.

DISCUSSION

This retrospective report provides first evidence for the feasibility of pancreatic adenocarcinoma treatment with the novel NTR1-targeted radiopharmaceutical ^{177}Lu-3BP-227. Tumor uptake was demonstrated in five of the six patients reported here (approx. 75% of pancreatic adenocarcinoma tumors express NTR1 (*3*). One patient with an extremely poor prognosis due to ascites formation achieved a partial remission of the disease and survived for 11 months after treatment initiation.

The kidneys were identified as the dose-limiting organ. However, none of the reported patients received a dose to the kidney that exceeded 23 Gy; the highest renal dose (22 Gy) was received by the patient obtaining a partial response. Taking into account that most pancreatic adenocarcinoma patients have a life expectancy shorter than the time it takes for radiation-induced kidney toxicity to develop (approx. 12 – 18 months), the dosimetric analysis of the patients in this report justifies prospective clinical trials to establish a safe and effective cumulative dose of ^{177}Lu-3BP-227 as well as risk factors to be considered in pancreatic adenocarcinoma patients.

One end-stage patient with massive ascites and a prognosis (given by the treating oncologist) of only a few weeks survival had an impressive response to intraperitoneal ^{177}Lu-3BP-227 TRLT with significant improvement in quality of life, general physical status, and emotional well-being. This patient survived for 13 months from the time of diagnosis, when ascites formation was already present, and for 11 months after the start of ^{177}Lu-3BP-227 TRLT. Compared to the median survival of pancreatic adenocarcinoma patients with new onset ascites of just 2 months (*2*), this constitutes a major improvement of survival, in particular in combination with the absence of any significant adverse effects. Although there was a short overlap with palliative chemotherapy, this only pertained to the initial dose of ^{177}Lu-3BP-227 to assess tumor uptake and dosimetry, and even in this setting, the administration of ^{177}Lu-3BP-227 did not elicit any acute side effects. The good tolerability of ^{177}Lu-3BP-227 TRLT is also demonstrated by the lack of any toxicity worse than reversible grade 2 anemia, which occurred in only one instance.

The major limitation of this report is the small and inhomogeneous patient population, which is due to the fact that this is a retrospective analysis of patients undergoing TRLT with ^{177}Lu-3BP-227 as last line of treatment after exhaustion of all conventional treatment options as opposed to a systematic clinical trial.

CONCLUSION

This report provides first clinical evidence of the feasibility of treatment of ductal pancreatic adenocarcinoma with the ^{177}Lu-labeled NTR1 antagonist 3BP-227. High uptake in metastatic tumor lesions and a promising toxicity profile warrant further investigation of ^{177}Lu-3BP-227 in prospective clinical studies to systematically evaluate the safety and efficacy of ^{177}Lu-3BP-227 and define the patient population benefitting most from ^{177}Lu-3BP-227 TLRT.

DISCLOSURES

Christiane Smerling, Frank Osterkamp and Ulrich Reineke are shareholders and employees of 3B Pharmaceuticals GmbH.

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Figures

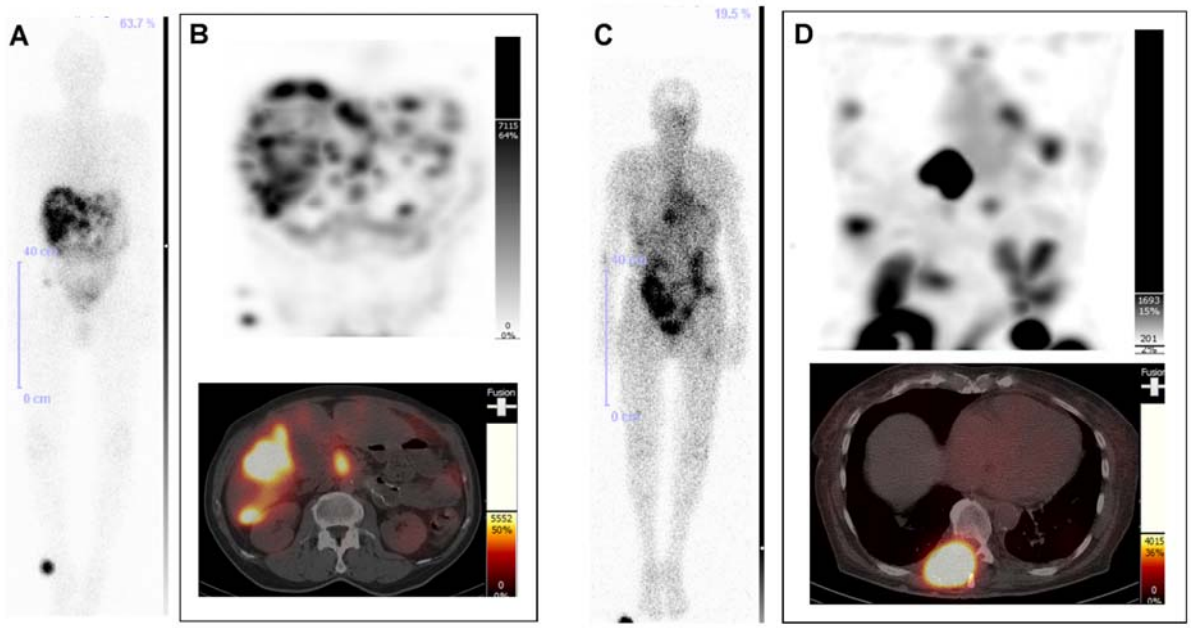


FIGURE 1. ^{177}Lu-3BP-227 planar and SPECT/CT scans of patient 1 (A-B) and patient 2 (C-D). (A) Planar scintigraphy 24 h p.i. (B) Upper panel: SPECT MIP 45 h p.i. Lower panel: Axial section, liver lesions and primary tumor, 45 h p.i. (C) Planar scintigraphy 48 h p.i. (D) Upper panel: SPECT MIP 44 h p.i. Lower panel: Axial section, large spinal lesion 44 h p.i.

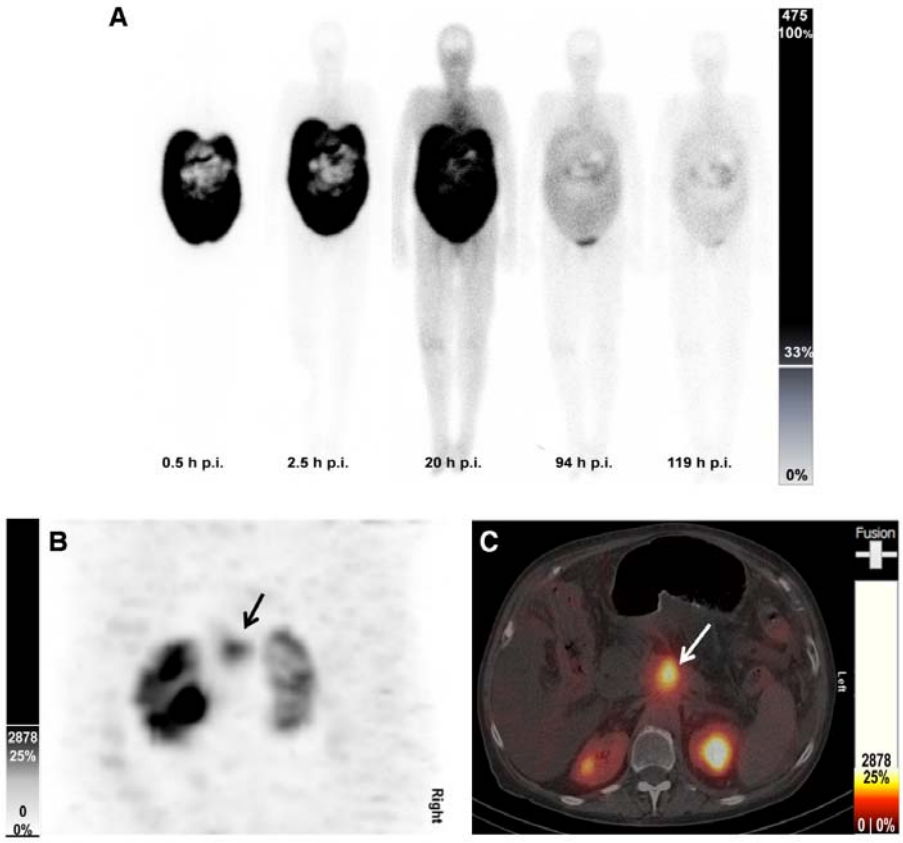


FIGURE 2. ^{177}Lu-3BP-227 planar and SPECT/CT scans of patient 3. (A) Series of whole-body images with corresponding count scale. (B) Maximum intensity projection 96 h after administration. Arrow indicates the primary tumor in the pancreatic body. (C) Axial section, primary tumor 96 h p.i.

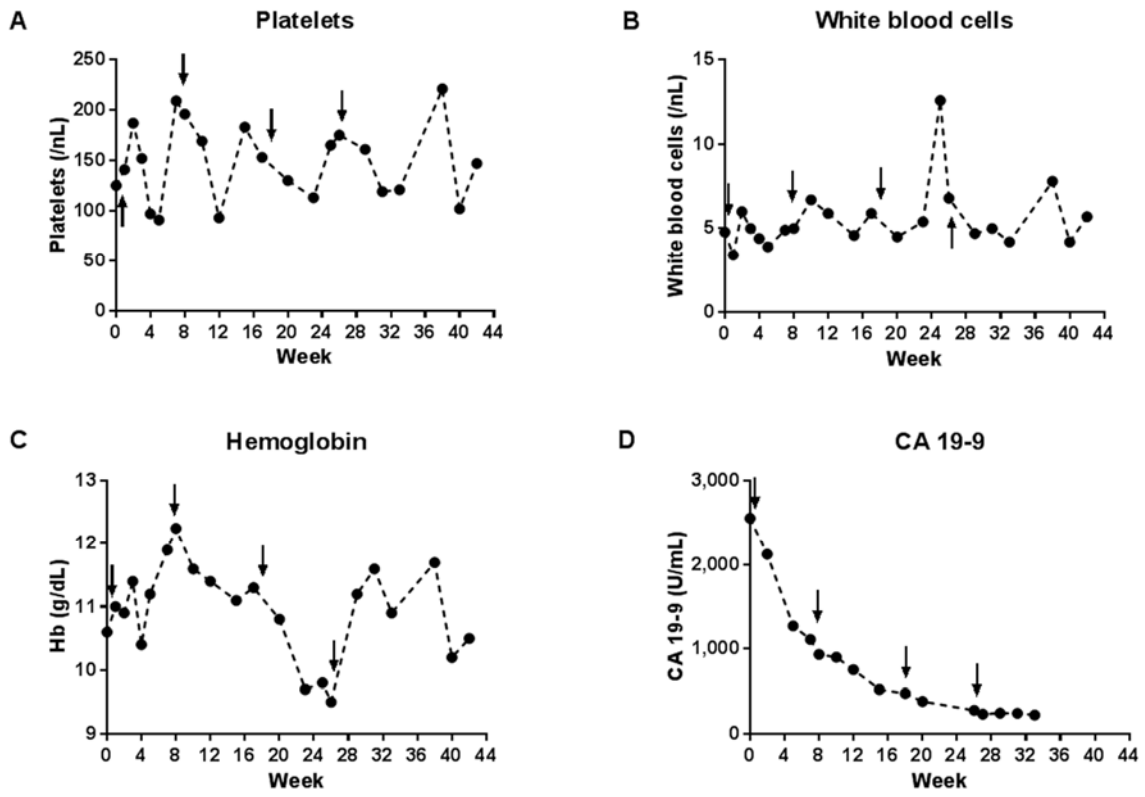


FIGURE 3. Laboratory parameters of patient 3 during ^{177}Lu-3BP-227 treatment and follow up. (A) Number of platelets. (B) Number of white blood cells. (C) Hemoglobin concentration. (D) Serum CA 19-9 levels. Arrows indicate TRLT cycles.

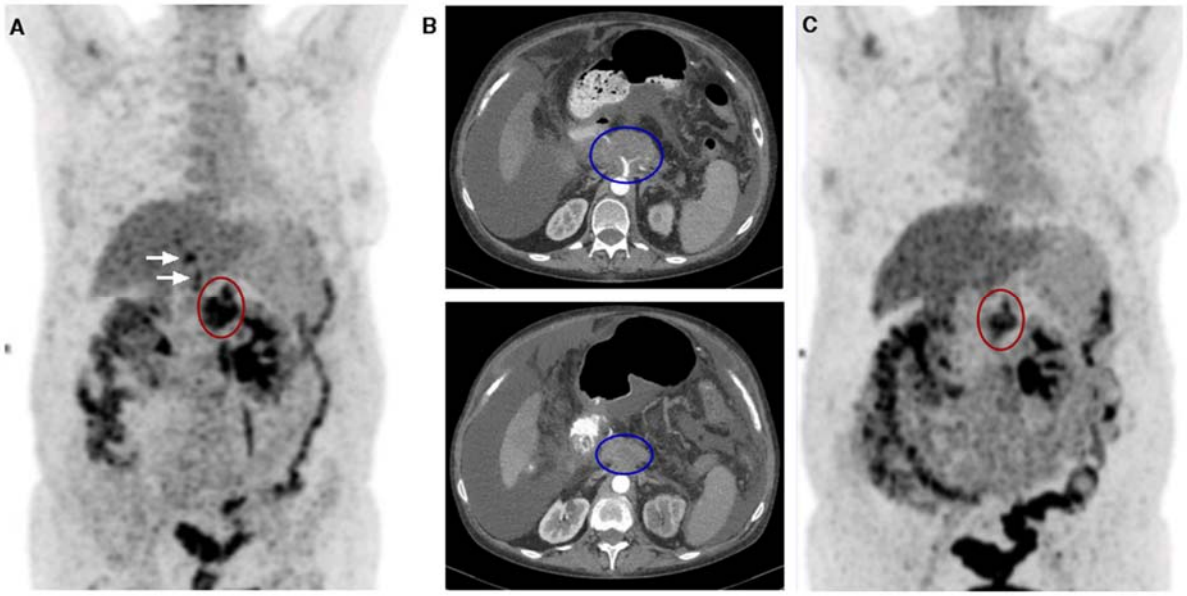


FIGURE 4. ^{18}FDG PET and CT scans of patient 3 before (A, B) and after (C, D) ^{177}Lu-3BP-227 therapy. (A) ^{18}FDG PET before ^{177}Lu-3BP-227 therapy. Red oval: primary tumor. Arrows: liver metastases. (B) Upper panel: Axial CT section; primary tumor (blue oval) before ^{177}Lu-3BP-227 therapy. Lower panel: Axial CT section; primary tumor (blue oval) after three cycles of ^{177}Lu-3BP-227 therapy. (D) ^{18}FDG PET after three cycles of ^{177}Lu-3BP-227 therapy. Red oval: primary tumor.

Tables

TABLE 1

Patient Demographic and Clinical Characteristics

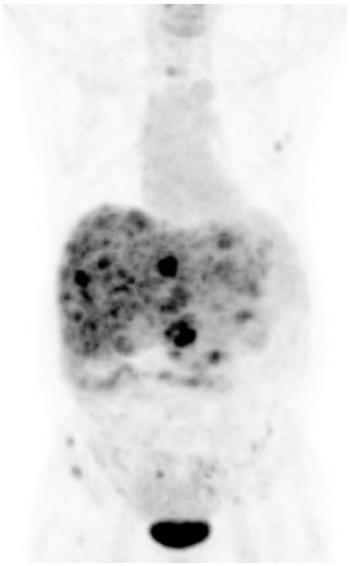
Variable	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6
Age (y)	59	75	59	57	61	74
Gender	M	F	F	M	F	M
Karnofsky performance status	50%	50%	70%	90%	90%	100%
Stage	IV	IV	IV	IV	IV	IV
Local extent	Infiltration of duodenum	Compression of the hepatobiliary duct	Infiltration of visceral blood vessels	Celiac trunk, superior mesenteric artery	None	Splenic hilum
Sites of metastases	Liver, bone, peritoneum	Liver, lungs, brain, lymph nodes, bone	Liver, lungs, lymph nodes, peritoneum	Liver, lymph nodes, peritoneum, bone	Liver, lymph nodes	Lung, adrenals, bone, muscle, stomach wall
Time from diagnosis (mo)	1	56	2	6	12	120
Prior therapy						
Chemotherapy		x	x	x	x	x
External radiation					x	x
Surgery				x		x
ERCP + stent	x			x		

TABLE 2
Absorbed Doses to Organs

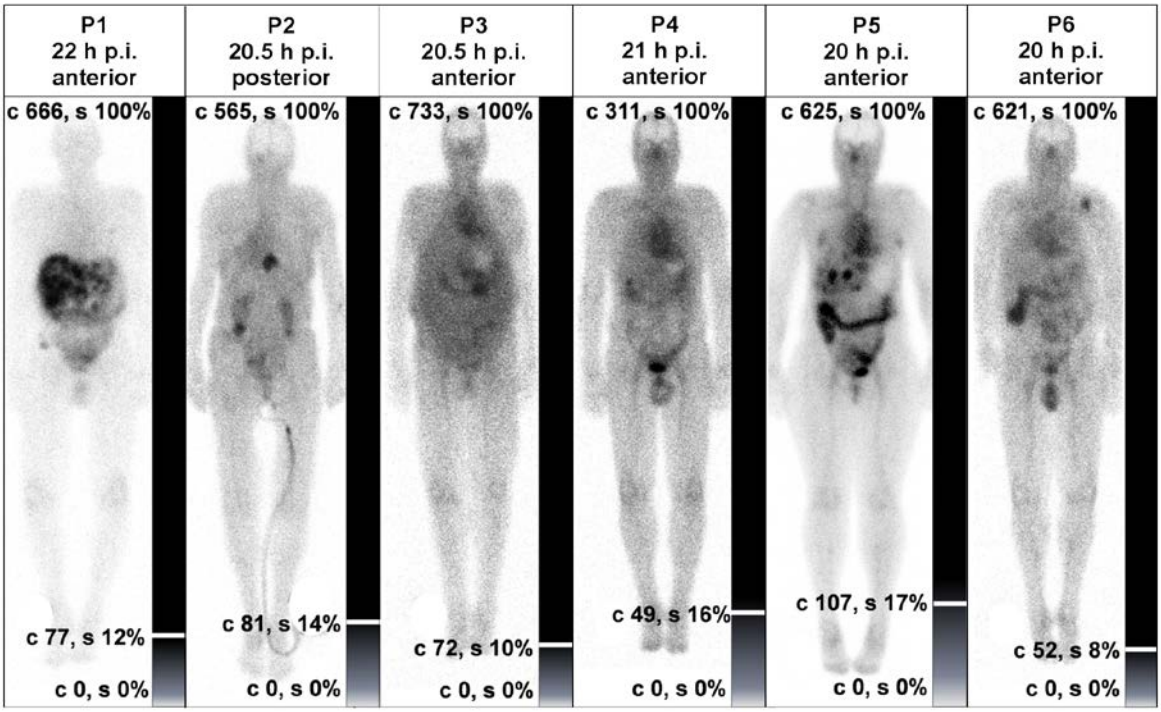
	Patient 1		Patient 2		Patient 3		
Target organ	**Gy/GBq**	**Total [Gy]**	**Gy/GBq**	**Total [Gy]**	**i.v. Gy/GBq**	**i.p. Gy/GBq**	**Total [Gy]**
Adrenals	0.09	0.104	0.07	0.104	0.07	0.09	1.937
Brain	0.08	0.096	0.07	0.099	0.06	0.09	1.813
Breasts	0.08	0.095	0.06	0.097	0.06	0.09	1.788
Gallbladder wall	0.09	0.103	0.07	0.103	0.06	0.09	1.911
Lower large intestinal wall	0.08	0.101	0.07	0.102	0.06	0.09	1.886
Small intestine	0.09	0.102	0.07	0.102	0.06	0.09	1.884
Stomach wall	0.08	0.101	0.07	0.102	0.06	0.09	1.884
Upper large intestinal wall	0.08	0.101	0.07	0.103	0.06	0.09	1.898
Heart wall	0.08	0.01	0.07	0.102	0.06	0.09	1.873
Kidneys	1.42	1.7	0.48	0.721	1.04	1.05	22.021
Liver	0.08	0.101	0.07	0.102	0.06	0.09	1.881
Lungs	0.08	0.098	0.07	0.101	0.06	0.09	1.854
Muscle	0.08	0.098	0.07	0.099	0.06	0.09	1.829
Ovaries	0.08	0.101	0.07	0.103	0.06	0.09	1.892
Pancreas	0.09	0.103	0.07	0.104	0.06	0.09	1.928
Red marrow	0.09	0.105	0.10	0.15	0.09	0.07	1.420
Osteogenic cells	0.26	0.317	0.25	0.378	0.23	0.29	6.005
Skin	0.08	0.094	0.06	0.096	0.06	0.09	1.769
Spleen	0.09	0.103	0.07	0.103	0.06	0.09	1.912
Testes	0.08	0.097					
Thymus	0.08	0.098	0.07	0.1	0.06	0.09	1.848
Thyroid	0.08	0.098	0.07	0.099	0.06	0.09	1.818
Urinary bladder wall	0.08	0.1	0.07	0.102	0.06	0.09	1.875
Uterus	0.08	0.101	0.07	0.102	0.06	0.09	1.886
Tumor lesions							
Pancreas (primary)	1	1.2			0.6	n.a.	17.8
Liver	45	54					
Bone 1	33	39.6					
Bone 2	53	63.6					
Spine			63	94.5			
Total body	0.09	0.106	0.07	0.106	0.07	0.10	1.948
Effective dose	0.09	0.104	0.07	0.104	0.07	0.09	1.937

SUPPLEMENTARY INFORMATION

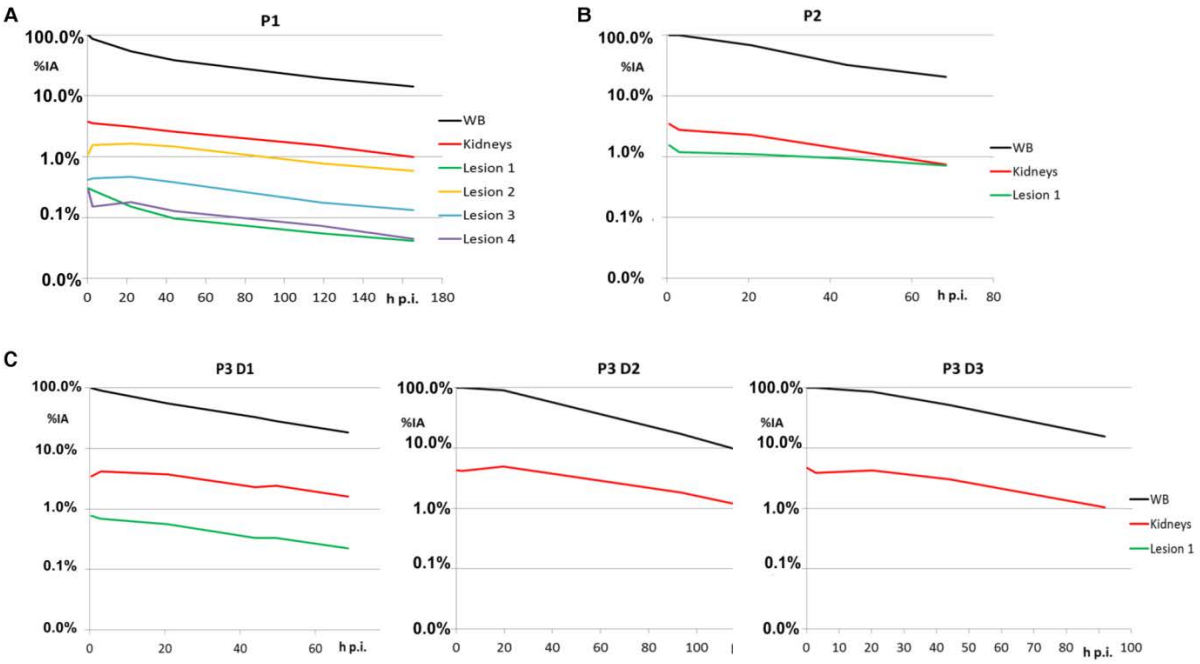
SUPPLEMENTARY FIGURES



SUPPLEMENTARY FIGURE 1. ^{18}F-FDG PET maximum intensity projection (MIP) image of patient 1 performed one day prior to the administration of ^{177}Lu-3BP-227.



SUPPLEMENTARY FIGURE 2. Whole body planar scintigraphies of all patients 20-22 h after administration of ^{177}Lu-3BP-227.



SUPPLEMENTARY FIGURE 3. Pharmacokinetics of ^{177}Lu-3BP-227 for whole-body (WB), kidneys, and lesions 1 to 4 in patient 1 (A) and lesion 1 in patient 2 (B). (C) Pharmacokinetics of patient 3 for first dosimetry study (D1) with primary lesion, and second (D2) and third (D3) without lesions.

SUPPLEMENTARY TABLE 1

Follow-up of hematological parameters

Patient Number	Applications				Date of death	Parameter	Hemoglobin (mmol/l)[§]		Leukocytes (Gpt/l)[§]		Thrombocytes (Gpt/l)[§]	
						Timepoint	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT
	Number	Type	RoA	Date		Test date	10/03/2014	14/03/2014	10/03/2014	14/03/2014	10/03/2014	14/03/2014
Patient 1	1	iDos	IV	12/03/2014	21/03/2014	Value	7.3	7.4	10.2	11.3	324	244
						Toxicity grade	G1	G1	G0	G0	G0	G0
						Date	27/09/2014	01/10/2014	27/09/2014	01/10/2014	27/09/2014	01/10/2014
Patient 2	1	iDos	IV	29/09/2014	02/11/2014	Value	7.2	6.6	20.2	15.1	304	205
						Toxicity grade	G1	G1	G0	G0	G0	G0
						Date	28/09/2014	10/10/2014	28/09/2014	10/10/2014	28/09/2014	10/10/2014
Patient 3	1	iDos	IV	29/09/2014		Value	6.6	11.4 (g/dl)	4.8	5.0 (nl)	141	152 (nl)
						Toxicity grade	G1	G1	G0	G0	G1	G0
						Date	18/11/2014	02/12/2014	18/11/2014	02/12/2014	18/11/2014	02/12/2014
	2	TRLT	IP	20/11/2014		Value	7.6	11.6 (g/dl)	5	6.7 (nl)	196	169 (nl)
						Toxicity grade	G1	G1	G0	G0	G0	G0
						Date	26/01/2015	10/02/2015	26/01/2015	10/02/2015	26/01/2015	10/02/2015
	3	TRLT	IP	28/01/2015		Value	6.7	10.8 (g/dl)	4.7	4.5 (nl)	147	130 (nl)
						Toxicity grade	G1	G1	G0	G0	G1	G1
						Date	23/03/2015	31/03/2015	23/03/2015	31/03/2015	23/03/2015	31/03/2015
	4	TRLT	IP	26/03/2015	25/08/2015	Value	5.9^	6.9	6.8	7	175	210
						Toxicity grade	G2	G1	G0	G0	G0	G0
						Date	28/01/2015	22/04/2015	28/01/2015	22/04/2015	28/01/2015	22/04/2015
Patient 4	1	iDos	IV	29/01/2015	01/01/2016	Value	6.5	6.9	2.4	6	77	122
						Toxicity grade	G1	G1	G2	G0	G1	G1
						Date	28/01/2015	02/02/2015	28/01/2015	02/02/2015	28/01/2015	02/02/2015
Patient 5	1	iDos	IV	29/01/2015		Value	5.5^	6.8	3.6	3.5	181	68
						Toxicity grade	G2	G1	G1	G1	G0	G2
						Date	22/02/2015	27/02/2015	22/02/2015	27/02/2015	22/02/2015	27/02/2015

	2	TRLT	IV	25/02/2015	20/05/2015	**Value**	6.4	7.1	6.2	10.4	238	244
						Toxicity grade	G1	G1	G0	G0	G0	G0
						Date	24/02/2015	01/06/2015	24/02/2015	01/06/2015	24/02/2015	01/06/2015
Patient 6	1	iDos	IV	25/02/2015		**Value**	8.0	7.4	10.8	12	196	293
						Toxicity grade	G1	G1	G0	G0	G0	G0
						Date	14/06/2015	02/07/2015	14/06/2015	02/07/2015	14/06/2015	02/07/2015
	2	TRLT	IV	15/06/2015	24/07/2015	**Value**	7.1	6.8	13.6	10.4	271	291
						Toxicity grade	G1	G1	G0	G0	G0	G0

TRLT, targeted radio-ligand therapy; iDos, initial activity administered for dosimetry and/or *in vivo* assessment; RoA, route of administration; [§] units for external laboratory values indicated in brackets along with their respective values; IV, intravenous; IP, intraperitoneal; ^ patient required 2 packed red blood cell transfusion before iDos/TRLT; Toxicity grade reported according to CTCAE v4.03

SUPPLEMENTARY TABLE 2

Follow-up of renal function parameters

Patient Number	Applications				Date of death	Parameter	Urea* (mmol/l)§		Creatinine (µmol/l)§		eGFR (ml/min/1.73m²)§	
						Timepoint	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT
	Number	Type	RoA	Date		Test date	10/03/2014	14/03/2014	10/03/2014	14/03/2014	10/03/2014	14/03/2014
Patient 1	1	iDos	IV	12/03/2014	21/03/2014	Value	9.6	14.2	84	79	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0
						Date	27/09/2014	NA	27/09/2014	09/10/2014	27/09/2014	09/10/2014
Patient 2	1	iDos	IV	29/09/2014	02/11/2014	Value	8.1	-	56	51	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0
						Date	28/09/2014	10/10/2014	28/09/2014	10/10/2014	28/09/2014	NA
Patient 3	1	iDos	IV	29/09/2014		Value	3.9	28 (mg/dl)	65	0.65 (mg/dl)	>60	-
						Toxicity grade	-	-	G0	G0	G0	-
						Date	18/11/2014	02/12/2014	18/11/2014	02/12/2014	18/11/2014	NA
	2	TRLT	IP	20/11/2014		Value	8.9	64 (mg/dl)	69	0.62 (mg/dl)	>60	-
						Toxicity grade	-	-	G0	G0	G0	-
						Date	26/01/2015	10/02/2015	26/01/2015	10/02/2015	26/01/2015	NA
	3	TRLT	IP	28/01/2015		Value	9.4	47 (mg/dl)	70	0.72 (mg/dl)	>60	-
						Toxicity grade	-	-	G0	G0	G0	-
						Date	23/03/2015	31/03/2015	23/03/2015	31/03/2015	23/03/2015	31/03/2015
	4	TRLT	IP	26/03/2015	25/08/2015	Value	10.9	4.2	71.5	71.9	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0
						Date	28/01/2015	22/04/2015	28/01/2015	22/04/2015	28/01/2015	22/04/2015
Patient 4	1	iDos	IV	29/01/2015	01/01/2016	Value	4.8	5.3	64	65.1	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0
						Date	28/01/2015	02/02/2015	28/01/2015	02/02/2015	28/01/2015	02/02/2015
Patient 5	1	iDos	IV	29/01/2015		Value	7.2	5.0	0.74	0.74	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0
						Date	22/02/2015	27/02/2015	22/02/2015	27/02/2015	22/02/2015	27/02/2015
	2	TRLT	IV	25/02/2015	20/05/2015	Value	3.8	8.3	65.8	71.1	>60	>60

						Toxicity grade	-	-	G0	G0	G0	G0
						Date	24/02/2015	01/06/2015	24/02/2015	01/06/2015	24/02/2015	01/06/2015
Patient 6	1	iDos	IV	25/02/2015		**Value**	5.9	4.8	74.5	107.3	>60	>60
						Toxicity grade	-	-	G0	G1	G0	G0
						Date	14/06/2015	18/06/2015	14/06/2015	18/06/2015	14/06/2015	18/06/2015
	2	TRLT	IV	15/06/2015	24/07/2015	**Value**	3.5	7.5	82	81	>60	>60
						Toxicity grade	-	-	G0	G0	G0	G0

TRLT, targeted radio-ligand therapy; iDos, initial activity administered for dosimetry and/or in-vivo assessment; RoA, route of administration; * not graded according to CTCAE; **§** units for external laboratory values indicated in brackets along with their respective values; IV, intravenous; IP, intraperitoneal; NA, not available; Toxicity grade reported according to CTCAE v4.03

SUPPLEMENTARY TABLE 3

Follow up of hepatic function parameters

Patient Number	Applications				Date of death	Parameter	Bilirubin (µmol/l)§		ALT (µmol/s/l)§		AST (µmol/s/l)§		GGT (µmol/s/l)§	
						Timepoint	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT	pre-iDos/TRLT	post-iDos/TRLT
	Number	Type	RoA	Date		Test date	10/03/2014	14/03/2014	10/03/2014	14/03/2014	10/03/2014	14/03/2014	10/03/2014	14/03/2014
Patient 1	1	iDos	IV	12/03/2014	21/03/2014	Value	156	229	1.78	2.36	1.56	2.06	57.67	62.07
						Toxicity grade	G3	G4	G2	G2	G1	G1	G4	G4
						Date	27/09/2014	NA	27/09/2014	NA	27/09/2014	NA	27/09/2014	NA
Patient 2	1	iDos	IV	29/09/2014	02/11/2014	Value	8	-	0.26	-	0.64	-	3.28	-
						Toxicity grade	G0	-	G0	-	G0	-	G2	-
						Date	28/09/2014	10/10/2014	28/09/2014	10/10/2014	28/09/2014	10/10/2014	28/09/2014	10/10/2014
Patient 3	1	iDos	IV	29/09/2014		Value	7	0.45 (mg/dl)	0.33	31 (U/l)	0.44	39 (U/l)	4.02	288 (U/l)
						Toxicity grade	G0	G0	G0	G0	G0	G1	G0	G3
						Date	18/11/2014	02/12/2014	18/11/2014	02/12/2014	18/11/2014	02/12/2014	18/11/2014	02/12/2014
	2	TRLT	IP	20/11/2014		Value	6	0.13 (mg/dl)	1.55	115 (U/l)	1.68	98 (U/l)	4.69	297 (U/l)
						Toxicity grade	G0	G0	G1	G2	G1	G1	G2	G3
						Date	26/01/2015	10/02/2015	26/01/2015	10/02/2015	26/01/2015	10/02/2015	26/01/2015	10/02/2015
	3	TRLT	IP	28/01/2015		Value	4	0.26 (mg/dl)	1.7	83 (U/l)	1.39	55 (U/l)	4.76	251 (U/l)
						Toxicity grade	G0	G0	G1	G1	G1	G1	G2	G3
						Date	23/03/2015	02/04/2015	23/03/2015	02/04/2015	23/03/2015	02/04/2015	23/03/2015	02/04/2015
	4	TRLT	IP	26/03/2015	25/08/2015	Value	4	2	0.73	0.51	0.31	0.26	2.86	2.42
						Toxicity grade	G0	G0	G1	G0	G0	G0	G1	G1
						Date	28/01/2015	22/04/2015	28/01/2015	22/04/2015	28/01/2015	22/04/2015	28/01/2015	22/04/2015
Patient 4	1	iDos	IV	29/01/2015	01/01/2016	Value	8	5	1.01	0.19	0.66	0.43	1.51	3.4
						Toxicity grade	G0	G0	G1	G0	G0	G0	G1	G2
						Date	28/01/2015	03/02/2015	28/01/2015	03/02/2015	28/01/2015	03/02/2015	28/01/2015	03/02/2015
Patient 5	1	iDos	IV	29/01/2015		Value	17	0.5 (mg/dl)	0.8	48 (U/l)	0.87	39 (U/l)	4.92	402 (U/l)
						Toxicity grade	G0	G0	G0	G1	G0	G1	G3	G4
						Date	22/02/2015	16/03/2015	22/02/2015	16/03/2015	22/02/2015	16/03/2015	22/02/2015	16/03/2015

	2	TRLT	IV	25/02/2015	20/05/2015	**Value**	4	0.3 (mg/dl)	0.64	32 (U/l)	0.74	39 (U/l)	7.65	594 (Ul)
						Toxicity grade	G0	G0	G0	G0	G0	G1	G3	G4
						Date	24/02/2015	01/06/2015	24/02/2015	01/06/2015	24/02/2015	01/06/2015	24/02/2015	01/06/2015
Patient 6	1	iDos	IV	25/02/2015		**Value**	7	5	0.28	0.16	0.48	0.29	3.05	3.65
						Toxicity grade	G0	G0	G0	G0	G0	G0	G2	G2
						Date	14/06/2015	05/07/2015	14/06/2015	05/07/2015	14/06/2015	05/07/2015	14/06/2015	05/07/2015
	2	TRLT	IV	15/06/2015	24/07/2015	**Value**	9	8	0.15	0.26	0.29	0.36	3.5	3.96
						Toxicity grade	G0	G0	G0	G0	G0	G0	G2	G2

TRLT, targeted radio-ligand therapy; iDos, initial activity administered for dosimetry and/or in-vivo assessment; RoA, route of administration; [§] units for external laboratory values indicated in brackets along with their respective values; IV, intravenous; IP, intraperitoneal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NA, not available; Toxicity grade reported according to CTCAE v4.03