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Title: Biodistribution and dosimetry results from a phase 1 trial of ^{177}Lu-lilotomab satetraxetan antibody-radionuclide-conjugate therapy

Johan Blakkisrud[1], Jon Erik Holtedahl[1] Ayca Løndalen[2] , Jostein Dahle[3] Tore Bach-Gansmo[2], Harald Holte[4], Stine Nygaard[4] , Arne Kolstad[4], Caroline Stokke[1,5]

[1]Department of Diagnostic Physics, Oslo University Hospital, Oslo, NORWAY

[2]Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, NORWAY

[3]Nordic Nanovector ASA, Oslo, NORWAY

[4]Department of Oncology, Radiumhospitalet, Oslo University Hospital, Oslo, NORWAY

[5]Oslo and Akershus University College of Applied Science, Oslo, NORWAY

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Corresponding author: Johan Blakkisrud, Department of Diagnostic Physics, Oslo University Hospital, Gaustad sykehus bygg 20, P.box 4959 Nydalen, 0424 Oslo, NORWAY, Telephone: (0047)481 46 588, Email: johbla@ous-hf.no

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ABSTRACT

^{177}Lu-lilotomab satetraxetan is a novel antibody radionuclide conjugate (ARC) currently in a phase 1/2a first-in-human dosage escalation trial for patients with relapsed CD37+ indolent non-Hodgkin lymphoma (NHL). The aim of this study was to investigate biodistribution and absorbed doses to organs at risk. ***Methods:*** A total of seven patients treated with ^{177}Lu-lilotomab satetraxetan were included for dosimetry. Patients were grouped based on two different pre-dosing regimens (with and without pre-dosing with 40 mg lilotomab) and were treated with different levels of activity per body weight (10, 15 and 20 MBq/kg). All patients were pre-treated with rituximab. Serial planar and SPECT/CT-images were used to determine time activity curves and patient specific masses for organs with ^{177}Lu-lilotomab satetraxetan uptake. Doses were calculated with OLINDA/EXM. ***Results:*** Organs with distinct uptake of ^{177}Lu-lilotomab satetraxetan, in addition to red bone marrow and tumors, were liver, spleen and kidneys. Largest uptake was found in the spleen, where doses ranged from 1.54 to 3.60 mGy/MBq. The liver received 0.70 to 1.15 mGy/MBq. The kidneys received the lowest dose of the source organs investigated; 0.16 to 0.79 mGy/MBq. No statistical significant differences in soft tissue absorbed doses for the two pre-dosing regimens were found. Whole body (WB) dose ranged from 0.08 to 0.17 mGy/MBq. ***Conclusion:*** The biodistribution study for patients treated with ^{177}Lu-lilotomab satetraxetan revealed highest physiological uptake in liver and spleen, besides red marrow. For all dosage levels investigated, doses were found modest when compared to commonly assumed tolerance limits.

Key words: biodistribution, antibody radionuclide conjugate, non-Hodgkin's lymphoma, internal dosimetry.

INTRODUCTION

Monoclonal antibodies have been used for many years in the targeting of cancer cells. Arming antibodies with radioisotopes is a means to direct ionizing radiation selectively at tumor sites in order to deliver clinically effective amounts of radiation to tumors while minimizing dose to normal tissues. The treatments are suited for systemic diseases, and especially for the radiosensitive lymphomas (*1,2*). Two radioimmunoconjugates (RICs) have been approved for treatment of NHL; ^{131}I-tositumomab or Bexxar© (GlaxoSmithKline LLC, Delaware, USA) and ^{90}Y-ibritumomab tiuxetan or Zevalin© (Spectrum pharmaceuticals, USA), both based on the CD20 antibody (*3*). Considering that these two RICs are most often used to treat patients who have already received rituximab, which also targets CD20, it is of interest to explore a new conjugate that targets a different antigen. The CD37 antigen is abundantly expressed on B-cells, but is absent on plasma cells and normal stem cells (*4,5*). Therefore, CD37 seems to be an appropriate therapeutic target in patients with relapsed B-cell derived malignancies.

RIT with CD37 as target has previously been explored clinically using a 131I-labeled murine monoclonal antibody (MB-1) (*6,7*). A higher degree of internalization and degradation of 131I-labeled RIC was found for CD37 than for CD20 (*8*). The potency of RIT against the internalizing antigen CD37 might have been underestimated by the use of a non-residualizing radionuclide in the early studies with 131I-MB-1 (*9*).

In recent years lutetium-177 has emerged as a favorable isotope for molecular radiotherapy. It has been used in clinical trials for diseases including adult neuroendocrine disease, prostate cancer and colorectal carcinoma (*10,11*) and is routinely used in peptide receptor radionuclide therapy (*12*). The beta-particles emitted by lutetium-177 have a mean energy of 0.13

MeV (half-life 6.7 days), and lutetium-177 mainly emits 113 keV (6%) and 208 keV (11%) photons (*13*). This is a major advantage, since these photons contribute little to excess radiation, but make post-therapy imaging feasible. Absorbed doses can therefore be retrospectively measured by quantification of the images. ^{177}Lu-lilotomab satetraxetan or Betalutin®(Nordic Nanovector ASA, Oslo, Norway) is a novel antibody-radionuclide conjugate that targets CD37. The ARC is currently under investigation in the phase 1/2a LYMRIT-37-01 trial for patients with relapsed CD37+ B-cell NHL (*14*). Red marrow and tumor doses have been previously reported for ^{177}Lu-lilotomab satetraxetan (*15,16*).

Here, seven of the patients treated with ^{177}Lu-lilotomab satetraxetan were included in a biodistribution and dosimetry protocol and subjected to more extensive imaging over the first week after administration. The aim of this work was to determine normal tissue absorbed doses for ^{177}Lu-lilotomab satetraxetan using the imaging data from this first-in-human trial.

MATERIAL AND METHODS

Patient Inclusion and Treatment

The phase 1 LYMRIT-37-01 trial is a non-randomized single injection dose finding study for treatment of relapsed indolent CD37+ NHL. Seven of the patients were included in the current biodistribution study. The trial was approved by the regional ethical committee and the patients were included upon written consent. Patients received a fixed amount of radioactivity per unit body weight (Table 1). Approximately 4-10 mg of radiolabeled antibody is injected in a typical patient (75 kg body mass, 15 MBq/kg), resulting in a specific activity of ^{177}Lu-lilotomab satetraxetan ranging approximately from 120 to 300 MBq per mg antibody. Patients in arm 1 (patient 2, 3 and 5) were pre-dosed with 40 mg lilotomab (cold CD37 antibody), patients in arm 2 (patient 13, 14 and 15), and patient 1 did not receive this pre-dosing (Fig. 1).

Image Acquisition

Patients underwent planar whole-body (WB) imaging and SPECT/CT at multiple time-points post administration of ^{177}Lu-lilotomab satetraxetan (Fig. 1). Scans were performed on a dual headed Siemens Symbia T16 SPECT/CT scanner equipped with a medium energy collimator using 2 x 32 projections, each of 45 seconds frame length in a non-circular orbit. A 20% window around 208 keV and a low scatter window of 20% of the 208 peak just below was used. The WB images were acquired with a 256x1024 matrix, and a scan speed of 5 cm/minute. A thin vacuum mattress on the examination table was used as a mean of fixation to ensure that the patients had the same position each time. The low dose CT was acquired over the total body length once such that it could be used for attenuation correction of the WB images. As a constancy control a vial with known activity of lutetium-177 was included alongside the patients.

Urine collection was performed separately during the first 2 hours and then the next 18 - 22 hours for patients 13 and 14.

Phantom Measurements and Scanner Calibration

Scanner calibration was performed using a large water-filled phantom with a smaller insert containing ^{177}Lu-lilotomab satetraxetan (103.6 MBq in 1.2 liter). A calibration factor of 39.1 Bq/count on the SPECT images was found from a volume of interest well inside the insert. This factor was validated by quantifying the known activities in an anthropomorphic Torso Phantom Model ECT/TOR/P (Data Spectrum Corporation, Durham, NC, USA). The phantom contained 3 inserts, "tumor" (20.5 MBq in 5 mL), "kidney" (13.6 MBq in 113 mL) and "spleen" (50.0 MBq in 106 mL), each filled with ^{177}Lu-lilotomab satetraxetan. The measurements resulted in relative errors of 3.3, -2.1 and 0.4%, respectively.

Data analysis and Quantification

For SPECT/CT-images the activities in the organs with distinct uptake (source organs) were found by manually drawing volumes of interests using PMOD 3.6 (PMOD Technologies Ltd, Zurich, Switzerland). SPECT-derived values were primarily used to determine organ kinetics. For time points where only planar imaging had been performed the planar-derived organ counts (see below) were adjusted according to the ratio between the planar counts and SPECT activity values day 4. The time-activity-curves (TAC) were calculated by interpolation between time points with a trapezoidal fit, and extrapolation after the last time point to a mono-exponentially curve based on day 4 and day 7. Activity at the first imaging point was assumed to represent the initial activity in a region. The time-integrated activity coefficients (TIACs) were calculated from the area under the TACs. TIACs for red marrow were retrieved from a separate work (*15*). Simulations investigating fewer imaging time points were performed by integrating

TACs after removal of time activity points. The individual organ volumes were found from delineating the organs using CT images day 4. A mass density of 1 g/ml was assumed.

For planar images, an in-house made MATLAB-program (version 2015a, MathWorks Inc, Natick, MA, USA) was used to automatically co-register the images using an intensity based registration. Counts in the organs at different time-points were found by manually drawing a region of interest around them at geometric mean images. This was done by three independent analysts and the mean of their results calculated. To correct for background activity a region nearby the organ region of interest was used for subtraction of counts. For the kidneys the background to organ activity ratios were generally low, occasionally resulting in negative counts, and therefore background correction for kidneys was omitted. Attenuation corrected planar images were also made and used for a parallel organ dose calculation.

The WB activity at 2 hours was assumed to represent the total injected activity. The WB activities at later time points were calculated using the planar images and normalization with the first time point. TAC fitting was performed mono-exponentially.

Dosimetry

Absorbed doses were calculated with the MIRD scheme (*17*). The individual time-integrated activity coefficients for each source organ (including WB and red marrow) were imported to OLINDA/EXM (version 1.1, Vanderbilt University, Nashville, TN, USA) for dose calculations. Standard adult male and female phantoms were used. The individual masses of the source organs were used as input. “Total body” mass was set to patient specific values without scaling the mass of remaining organs. For the rest of the organs the default phantom values in OLINDA/EXM were used.

Statistics

Absorbed doses for patients with and without pre-dosing were compared with a two-sided student t-test.

RESULTS

Biodistribution and Absorbed Doses

By visual inspection of the activity distribution tumor, spleen, liver, bone marrow and kidneys were determined to have distinct uptake of ^{177}Lu-lilotomab satetraxetan and categorized as source organs (Fig. 2). The effective WB half-life of ^{177}Lu-lilotomab satetraxetan was similar across the population (TACs in Fig. 3D), with a mean value of 82 hours (ranging from 72 to 95 hours). The activity excreted via urine before the first planar scan was 21 MBq and 9 MBq (1.4 and 0.9% of the injected activity) for patient 13 and 14, respectively. This indicates that only marginal errors are introduced by assuming that all injected activity is retained at the first WB imaging time point, this assumption was therefore used for all patients.

Spleen received the highest organ doses with a mean value of 2.92 Gy and the max observed value was 6.50 Gy (Table 2). The liver and kidneys received a max dose of 2.00 Gy and 0.62 Gy, respectively. No adverse events related to kidney or liver function have been reported for patients who received ^{177}Lu-lilotomab satetraxetan with a follow-up of 15 – 50 months.

Table 3 sums up the absorbed dose per unit administered activity values for the two arms, here including patient 1 with arm 2. Average values across all patients were determined to 2.92 mGy/MBq, 0.92 mGy/MBq and 0.35 mGy/MBq for spleen, liver and kidneys, respectively. WB doses were 0.12 mGy/MBq and 0.14 mGy/MBq for pre-dosed and non-pre-dosed respectively. A conservative calculation using reference total body masses instead of patient specific values would change the total body doses to 0.16 and 0.15 mGy/MBq. The difference in dose per injected activity for spleen, kidneys, liver and WB between pre-dosed and non-pre-dosed patients

was not significant (lowest P-value = 0.24). The pre-dosed patients received a lower dose to the RM than non-pre-dosed patients (P = 0.05). For the other organs, which had less uptake of ^{177}Lu-lilotomab satetraxetan, the doses were calculated using OLINDA/EXM. The doses to these are primarily the result of beta-radiation from the assumed uniform remaining WB distribution of activity not assigned to the source organs.

Methodological Evaluations

Various aspects of the dose calculation were investigated. Care was taken to apply the same resulting methods for all patients.

The common assumption of a constant ratio between the SPECT/planar images over time was explored using the additional SPECT data from day 7. An average agreement of 9% (+/- 5%) between the planar value day 7 corrected by ratio planar-to-SPECT day 4, and the direct measurement from SPECT day 7 was found in patients from arm 1 and 2. This deviation was considered to contribute to substantial errors in the TAC calculation, and therefore SPECT derived data were primarily used for all patients.

TIACs for the source organs in arm 1 were compared using attenuation corrected vs non-attenuation corrected planar images; the deviations were within 1%. For WB the deviations were within 3%. As the relative planar values are adjusted by absolute organ values obtained from SPECT/CT (or injected activity for WB) and the planar correction matrix is constant in time, the minor differences between corrected and non-corrected image sets can most likely be explained by alignment errors of the attenuation correction matrix. Attenuation correction of planar images was therefore omitted for all patients.

Supplementary figure 1 shows the difference in the calculated doses for arm 1 patients if a reduced number of imaging time points had been obtained. Removal of the 4 h and 8 h time points led to deviations no greater than 1%, and these two imaging points were therefore removed in arm 2.

DISCUSSION

This biodistribution and dosimetry study has been a part of a phase 1/2a trial of ^{177}Lu-lilotomab satetraxetan for treatment of NHL, which is the first-in-human study of this ARC. For all activity dosage levels and the two pre-dosing regimens investigated the absorbed doses to liver, spleen and kidneys were within commonly assumed tolerance levels. Accordingly, no signs of non-hematological toxicities were observed after treatment.

^{177}Lu-lilotomab satetraxetan is seen in the blood and heart at 2 hours after injection, and uptake in liver and kidneys is also visible at this early time point (Fig. 2). Peak spleen levels can be estimated to occur at a later time point some days after administration of ^{177}Lu-lilotomab satetraxetan (Fig. 3). A relatively low proportion of the activity distributes to kidneys compared to some previously investigated RICs, probably demonstrating the larger molecular weight of the ARC and/or stronger binding of the radiometal lutetium-177 to the antibody.

Pre-clinical studies suggested that red marrow, liver, spleen and kidneys were the organs receiving the higher doses, and red marrow to be the critical organ for ^{177}Lu-lilotomab satetraxetan treatment (*14*). The clinical dosimetry results fit well with the pre-clinical findings. For liver and kidneys, the absorbed doses are far below the external beam radiation therapy tolerance levels and the suggested levels from i.e. ^{177}Lu-DOTATATE treatment (*18, 19*). However, the variances in dose-rate, energy, and other factors for different treatments suggest that tolerance limits should be verified empirically for new therapies. Preliminary clinical findings for ^{177}Lu-lilotomab satetraxetan have shown that adverse events are limited to hematological toxicities (*20*). The observed correlation between red marrow dose and thrombocytopenia for these patients is previously discussed (*15*). The lack of other adverse

events supports that the reported kidney and liver doses are well within tolerance limits for ^{177}Lu-lilotomab satetraxetan therapy. Radiation induced effects of spleen irradiation may include hematological effects, and investigations for ^{177}Lu-DOTATATE treatment have suggested that spleen doses can contribute to hematological toxicity (*21*). However, the evidence indicates that doses no higher than 6.5 Gy (max dose found in the present study, Table 2) are too low to introduce such effects (*21*,*22*). Isolating theoretical contributions from spleen irradiation to the hematological adverse events is therefore difficult for ^{177}Lu-lilotomab satetraxetan treatment.

The organs receiving the highest doses in RIC therapy for lymphoma are typically spleen, liver, kidneys and bone marrow (*6*,*23*-*26*). Two anti-CD20 RICs, ^{90}Y-ibritumomab-tiuxetan and ^{131}I-tositumomab, have been approved by the Food and Drug Administration for treatment of NHL. It is therefore relevant to compare doses between these treatments and ^{177}Lu-lilotomab satetraxetan therapy. ^{131}I-tositumomab is administered to limit the WB dose to 75 cGy (*27*). The amount of ^{90}Y-ibritumomab-tiuxetan is administrated based on patient body weight (15 MBq/kg) limited by a maximum activity of 1,200 MBq (*28*). The expected organ and WB doses for ^{90}Y-ibritumomab-tiuxetan, ^{131}I-tositumomab and a ^{177}Lu-lilotomab satetraxetan treatment regimen for a hypothetical 80 kg patient are compared in Table 4. The ^{177}Lu-lilotomab satetraxetan dosage level is chosen based on preliminary clinical results and maximum tolerated activity levels. The comparison indicates that ^{177}Lu-lilotomab satetraxetan doses will mostly be equal to or lower than typical ^{90}Y-ibritumomab-tiuxetan or ^{131}I-tositumomab absorbed doses. However, a more clinically relevant comparison could be considered to compare absorbed doses between iso-effective treatment administrations, instead of simply the prescribed values, and the results should therefore be interpreted with care.

For targeted molecular radiotherapies of NHL, patient-specific dosage regimes based on administration of a pre-therapy tracer activity has been explored. The therapeutic amounts of ^{131}I-tositumomab to be delivered were calculated from tracer biodistribution of each patient. However, for ^{90}Y-ibritumomab-tiuxetan, a surrogate ^{111}In-ibritumomab tiuxetan tracer did not estimate absorbed radiation doses that were correlated with toxicity of the treatment. Dosage based on body weight and platelet counts were therefore preferred (*29*). The low gamma yield of lutetium-177 is sufficient for post-therapy imaging but discourages the use of a tracer amount of ^{177}Lu-lilotomab satetraxetan upfront of a treatment to calculate the maximum tolerated activity. A possible solution could be to substitute the lutetium-177 with a more gamma intense isotope or a positron emitter.

In the present study, quantification was predominantly based on SPECT/CT, as the quantifications of phantom insertions solely on planar images demonstrated deviations of up till 35% (data not shown, background and attenuation corrected geometric mean images with use of calibration source). Differences between a 2D and 3D protocol for ^{90}Y-ibritumomab-tiuxetan have been investigated, and systematically lower 3D-derived doses were found for the liver and spleen (*30*). They argued that although a supporting single SPECT/CT improved the accuracy of the calculation, a full 3D-approach should be preferred. This is also our conclusion for ^{177}Lu-lilotomab satetraxetan, given the observed non-consistent ratio of planar-to-SPECT-derived activity. The latest MIRD pamphlet also recommends SPECT/CT for dosimetry of lutetium-177 based therapies (*31*).

The doses to liver, spleen, kidney and WB were not significantly different from the pre-dosed (40 mg lilotomab) to the non-pre-dosed group. Mean kidney doses were lower in non-pre-dosed patients, and spleen doses tended to be higher. This could be explained by higher uptake of

^{177}Lu -lilotomab satetraxetan in some organs (including spleen and red marrow), leading to lower cumulated blood activities, and lower renal excretion in the non-pre-dosed group. A significant difference in red marrow absorbed dose between pre-dosed and non-pre-dosed patients was observed both for the current group of patients and a larger group discussed in our previous work (*15*). Pre-dosing as a means to improve biodistribution has been used for other ARCs. The amount of pre-dosing investigated in the current study (40 mg lilotomab) is modest compared to the amounts used for ^{90}Y-ibritumomab-tiuxetan (250 mg/m^2 ibritumomab) and ^{131}I-tositumomab (450 mg tositumomab) (28, 32). However, based on *in vitro* results, the current pre-dosing with lilotomab is 2-10 times the required amount to block 95-97 % of CD37 positive cells (data not shown). In this clinical trial, pre-dosing of 40 mg lilotomab (4-10 times the amount of administered ^{177}Lu-lilotomab satetraxetan) has been shown to give a significant lowering of RM doses. The optimal amount of pre-dosing for protection of RM is currently under investigation. While it would be interesting to further investigate potential differences using a larger patient material for liver, spleen and kidneys, the clinical need is lessened by the observation that these organs (unlike red marrow) are unlikely to be critical organs for the ^{177}Lu-lilotomab satetraxetan treatment.

CONCLUSION

Normal tissue doses for liver, spleen, kidney and WB were lower than assumed tolerance limits for patients treated with amounts of ^{177}Lu-lilotomab satetraxetan up till the maximum tolerated activities defined by myelosuppression. Methodological investigations suggest a full 3D-imaging based approach to be the most accurate. There were no significant differences in absorbed dose to soft tissue organs between patients with and without pre-dosing with 40 mg lilotomab. Our findings support that red marrow is the critical organ for ^{177}Lu-lilotomab satetraxetan therapy, and that monitoring dose to soft tissue organs may be redundant in ordinary clinical practice.

DISCLOSURE

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TABLES

TABLE 1: Patients included in the biodistribution and dosimetry study. R: pre-treated with rituximab, R+L: pre-treated with rituximab and pre-dosed with lilotomab.

Patient number	Sex	Pre-treatment and pre-dosing	Dosage level [MBq/kg]	Body weight [kg]	Injected activity [MBq]
001	F	R	10	118	1,102
002	M	R+L	10	103	1,036
003	M	R+L	10	73	746
005	M	R+L	20	97	1,982
013	M	R	15	94	1,416
014	F	R	15	71	1,013
015	M	R	10	113	1,120

TABLE 2. Individual absorbed dose, mass and time-integrated activity coefficient (TIAC) for the target organs. The different shadings separate the pre-treatment and pre-dosing regimens.

Organ	Patient number	Mass	TIAC	Dose
		(g)	(h)	(Gy)
Liver	001	1,876	14.62	0.77
	002	2,405	19.84	0.77
	003	1,295	16.74	0.86
	005	1,705	19.38	2.00
	013	1,690	20.03	1.49
	014	1,687	19.05	1.04
	015	2,030	17.8	0.79
Spleen	001	262	7.97	2.92
	002	406	7.15	1.60
	003	100	4.15	2.69
	005	194	7.34	6.50
	013	170	6.76	4.89
	014	152	5.55	3.21
	015	187	5.96	2.77
Kidney	001	204	0.67	0.33
	002	233	0.70	0.29
	003	117	1.05	0.59
	005	270	0.93	0.62
	013	211	0.69	0.42
	014	147	0.47	0.30
	015	282	0.47	0.16

TABLE 3: Absorbed doses to all organs for the different treatment regimens.

	With lilotomab pre-dosing	Without lilotomab pre-dosing
	Mean (range) mGy/MBq	Mean (range) mGy/MBq
Adrenals	0.12 (0.1-0.14)	0.09 (0.07-0.12)
Brain	0.10 (0.08-0.13)	0.07 (0.05-0.10)
Breasts	0.10 (0.08-0.12)	0.07 (0.05-0.10)
Gallbladder Wall	0.12 (0.10-0.14)	0.09 (0.07-0.12)
LLI Wall	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Small Intestine	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Stomach Wall	0.11 (0.09-0.13)	0.08 (0.06-0.11)
ULI Wall	0.11 (0.09-0.14)	0.08 (0.06-0.11)
Heart Wall	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Kidneys	0.46 (0.28-0.79)	0.27 (0.16-0.30)
Liver	0.97 (0.74-1.15)	0.89 (0.70-1.05)
Lungs	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Muscle	0.1 (0.08-0.13)	0.08 (0.06-0.10)
Ovaries	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Pancreas	0.12 (0.10-0.14)	0.1 (0.07-0.12)
Osteogenic Cells	0.50 (0.31-0.70)	0.81 (0.63-1.03)
Red Marrow	0.91 (0.63-1.18)	1.51 (1.39-1.78)
Skin	0.10 (0.08-0.12)	0.07 (0.05-0.09)
Spleen	2.81 (1.54-3.6)	3.01 (2.65-3.45)
Testes	0.10 (0.08-0.13)	0.07 (0.05-0.10)
Thymus	0.11 (0.09-0.13)	0.08 (0.06-0.10)
Thyroid	0.10 (0.08-0.13)	0.07 (0.05-0.10)
Urinary Bladder Wall	0.11 (0.09-0.13)	0.08 (0.06-0.10)
Uterus	0.11 (0.09-0.13)	0.08 (0.06-0.11)
Total Body	0.14 (0.12-0.17)	0.12 (0.08-0.15)

TABLE 4: Doses for ^{90}Y-ibritumomab-tiuxetan and ^{131}I-tositumomab compared to ^{177}Lu-lilotomab satetraxetan.

	^{90}Y-ibritumomab-tiuxetan*	^{131}I-tositumomab †	^{177}Lu-lilotomab satetraxetan 20 MBq/kg + lilotomab pre-dosing
	(Gy)	(Gy)	(Gy)
Liver	5.76	2.56	1.55
Spleen	11.28	3.56	4.50
Kidney	0.12	6.1	0.74
WB	0.6	0.75	0.22
Red marrow/Marrow space	1.56	2.03	1.46

* (*28*) – A patient of 80 kg and 15 MBq/kg administered activity are assumed.

† (*32*) – Administered activity to limit the WB dose to 0.75 Gy is assumed.

FIGURE LEGENDS

FIGURE 1: Pre-treatment, pre-dosing and imaging protocol Different pre-dosing and pre-treatment regimens are shown in parallel. The zero-hour timepoint of the non-linear timeline is set according to the injection of ^{177}Lu-lilotomab satetraxetan. The boxes labeled "Planar" represent whole body planar scintigraphs, and subsequent SPECT/CT acquisition is also indicated.

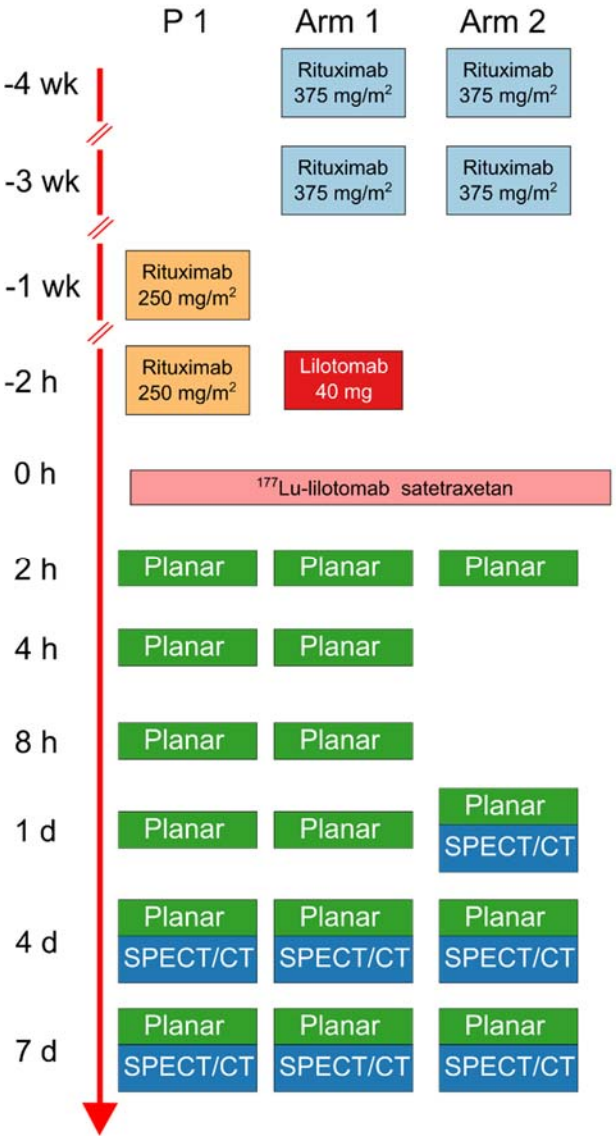


FIGURE 2: Planar (anterior and posterior, four time points) and SPECT/CT images (MIP, three time points) of patient 14 after injection of ^{177}Lu-lilotomab satetraxetan. Activity in the blood can be seen at early time points, with gradual uptake and following wash-out in liver, spleen and bone marrow. Uptake in inguinal tumors is also visible.

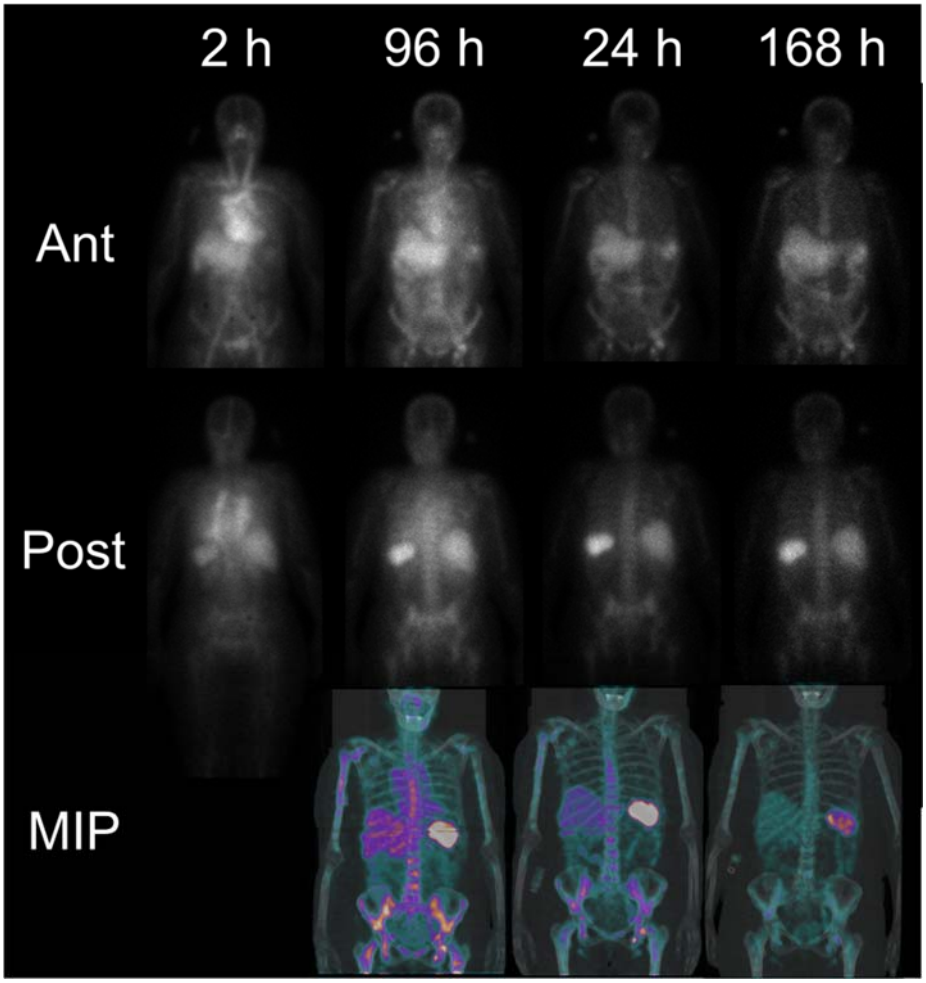
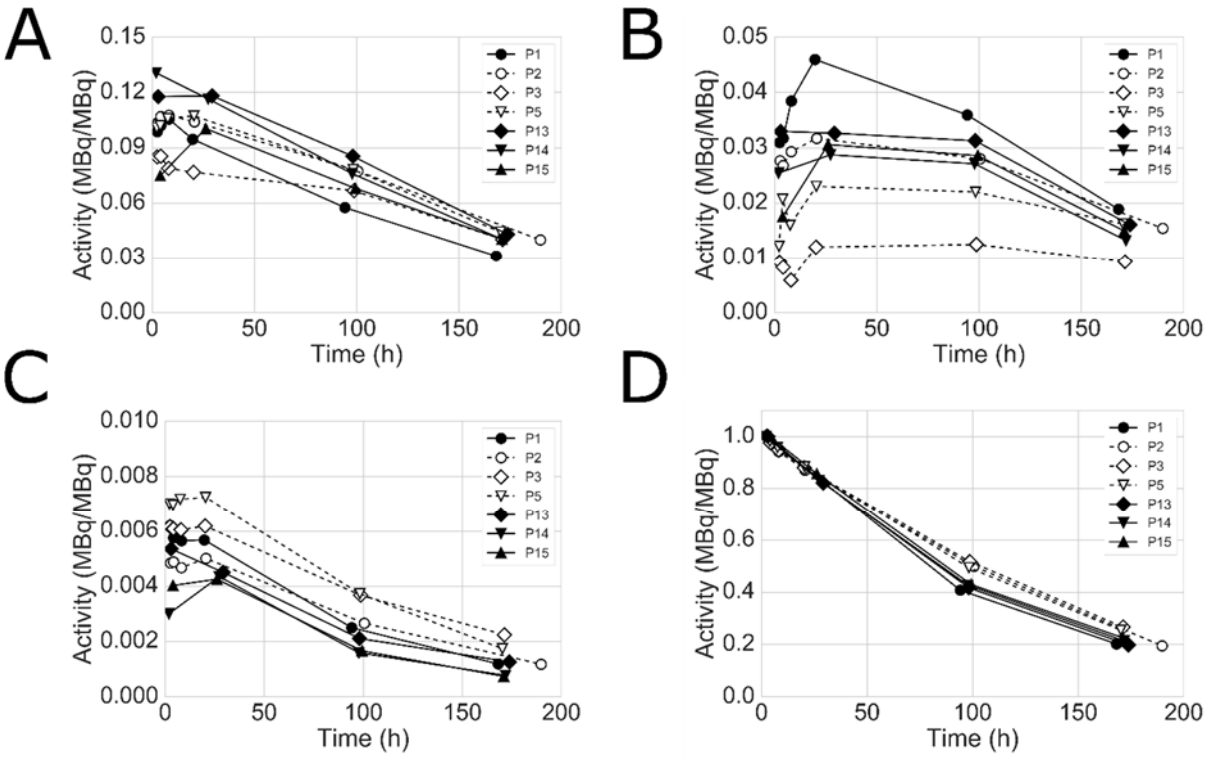
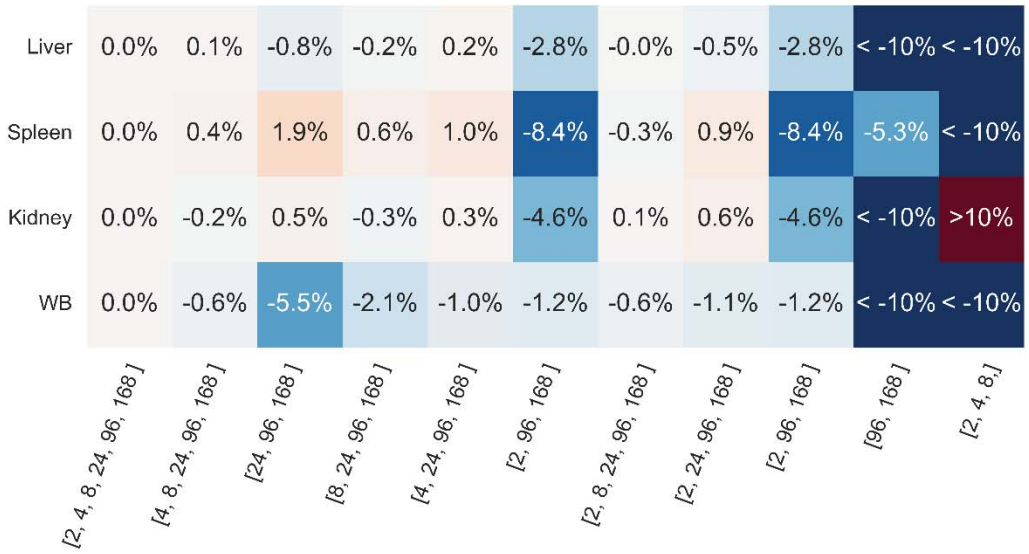


FIGURE 3. Time activity curves showing the uptake and clearance in liver, spleen, and kidney (A-C, respectively) and the whole body (D) for individual patients. The measured activity is normalized by injected activity. Decay correction is not performed.



Supplementary

Supplementary Fig 1. Percentage errors of the TIACs introduced for protocols with a reduced number of imaging time points (indicated as hours p.i) compared to the original six time point protocol (2, 4, 8, 24, 96 and 168 hours p.i.). The numbers in brackets are the included time points in units of hours p.i. The integral is calculated as described in the article. Largest errors across patient 1-5 are shown. The color scale reflects the magnitude of the error from -10 to 10 %. Error above 10 % or undefined integrals are written as ">10 %" Protocol (2, 24, 96 and 168 hours p.i.) was chosen for arm 2. An interactive figure can be found as Supplementary file 2.



Biodistribution and dosimetry results from a phase 1 trial of ^{177}Lu-lilotomab satetraxetan antibody-radionuclide conjugate therapy

Johan Blakkisrud, Jon Erik Holtedahl, Ayca Løndalen, Jostein Dahle, Tore Bach-Gansmo, Harald Holte, Stine Nygaard, Arne Kolstad and Caroline Stokke

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