Journal of Nuclear Medicine, published on May 18, 2018 as doi:10.2967/jnumed.118.210997

Feasibility of CXCR4-directed radioligand therapy in advanced diffuse large B cell lymphoma

Constantin Lapa[1], Heribert Hänscheid[1], Malte Kircher[1], Andreas Schirbel[1], Gerd Wunderlich[2], Rudolf A. Werner[1], Samuel Samnick[1], Jörg Kotzerke[2], Hermann Einsele[3], Andreas K. Buck[1], Hans-Jürgen Wester[4], Götz Ulrich Grigoleit[3]

[1]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany
[2]Department of Nuclear Medicine, University Hospital Dresden, Dresden, Germany
[3]Department of Internal Medicine II, Division of Hematology and Medical Oncology, Universitätsklinikum Würzburg, Würzburg, Germany
[4]Pharmaceutical Radiochemistry, Technische Universität München, Munich, Germany

Running title: CXCR4-directed RLT in DLBCL

Word counts:

Corresponding author:
Constantin Lapa, MD
Department of Nuclear Medicine
Universitätsklinikum Würzburg
Oberdürrbacher Str. 6
97080 Würzburg
Germany
Phone: +49 - 931-2013412
Email: lapa_c @ukw.de

Key words: chemokine receptors; CXCR4; lymphoma; DLBCL; radioligand therapy

Abstract:

We have recently reported on our experience with C-X-C-motif chemokine receptor 4- (CXCR4-) directed radioligand therapy (RLT) in multiple myeloma and acute leukemia.

Methods: Six patients with heavily pre-treated relapsed diffuse large B cell lymphoma (DLBCL) (3 males, 3 females; aged, 54±8 years) underwent CXCR4-directed RLT in combination with conditioning chemotherapy and allogeneic stem cell transplantation (SCT). In 2 patients, radioimmunotherapy (RIT) targeting CD20 or CD66 was added to enhance anti-lymphoma activity. Endpoints were incidence and severity of adverse events, progression-free and overall survival.

Results: RLT as well as additional RIT were well-tolerated without any acute adverse events or changes in vital signs. Successful engraftment was recorded after a median of 11 days (range, 9-13 d). In the 4 patients who were available for follow-up (one patient died of CNS aspergillosis 29 days, another of sepsis in aplasia 34 days after after RLT), CXCR4-directed RLT resulted in partial response in 2/4 cases (both treated with additional RIT) and mixed response in the remaining 2 subjects. Response duration was rather short-lived with median progression-free survival of 62 days (range, 29-110 d) and median overall survival of 76 days (range, 29-313 d).

Conclusions: CXCR4-directed RLT (in combination with additional RIT) as a conditioning regimen prior to allogeneic SCT in DLBCL is feasible.

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma accounting for approximately 25% of all cases (*1*). Systemic chemotherapy, immunotherapy with the recombinant anti-CD20 antibody rituximab and external radiotherapy are the mainstay of therapy and achieve 10-year survival rates of 40-50% (*2*). However, patients with refractory or relapsed disease have a worse prognosis and second-line chemotherapy is administered to achieve a second response prior to high-dose chemotherapy and subsequent stem cell transplantation (SCT).

C-X-C-motif chemokine receptor 4 (CXCR4) is overexpressed on lymphoma cells (*3-6*) and has been identified as a potential drug target. Wester and co-workers successfully developed a radiolabelled CXCR4-ligand (^{68}Ga-Pentixafor) for positron emission tomography (PET) imaging (*5,7,8*) that could be demonstrated to visualize CXCR4-expression in patients with hematologic as well as solid malignancies (*5,9-17*). Recently, we and others also reported on the experience with ^{177}Lu- and ^{90}Y-labelled Pentixather ((*18*); ^{177}Lu-Pentixather and ^{90}Y-Pentixather), the therapeutic counterpart of ^{68}Ga-Pentixafor for CXCR4-targeted radioligand therapy (RLT) in acute leukemia (*19*) and in patients with advanced multiple myeloma (*20,21*). In this manuscript, we evaluate the feasibility of CXCR4-directed RLT as part of the conditioning regimen prior to allogeneic SCT in patients with relapsed, very advanced-stage DLBCL.

MATERIAL and METHODS

Subjects

Six patients (3 male, 3 female; aged, 54±8 years) with relapsed, refractory DLBCL were included into the study. All patients had undergone multiple lines of previous treatment (2-6 lines of treatment, median 3 lines) and presented with refractory, progressive disease.

Given the lack of alternative treatments in this advanced disease stage, experimental CXCR4-directed treatment was offered to the patients on a compassionate use basis (German Drug Act, §13,2b) in compliance with §37 of the Declaration of Helsinki as part of the conditioning regimen prior to repeated allogeneic SCT. Treatment was approved by the clinical ethics committee of our institution. All subjects gave written informed consent prior to therapy. Patient characteristics are depicted in Table 1.

^{68}Ga-Pentixafor Imaging

CXCR4-expression was confirmed in all patients using ^{68}Ga-Pentixafor PET/computed tomography (CT) using a dedicated PET/CT scanner (Siemens Biograph mCT 64; Siemens Medical Solutions, Erlangen, Germany). CXCR4-directed PET/CT imaging was performed 60 minutes after injection of 62 to 165 MBq (median, 95 MBq) of ^{68}Ga-Pentixafor as previously described (*21*). ^{68}Ga-Pentixafor positive lesions were visually determined as focally increased tracer retention as compared to surrounding normal tissue or contralateral structures.

Pre-therapeutic Dosimetry and CXCR4-directed Radioligand Therapy

RLT was preceded in every patient by a pre-therapeutic dosimetry study with 200 MBq of ^{177}Lu-Pentixather intended to identify critical organs and the safely administrable activities and to estimate the achievable tumor doses as outlined in (*21*).

Based on their individual dosimetry, patients were treated by intravenous injection of ^{90}Y-labeled Pentixather (see Table 2). ^{90}Y-Pentixather was used for treatment in order to enhance cross irradiation of

potential areas of reduced uptake in extramedullary lesions and, more importantly, to shorten the time interval to SCT. With its 64 h physical half-life, ^{90}Y activity and thus the residual absorbed dose is reduced to 2.6% of the total absorbed dose after 2 weeks by physical decay only. The effective half-life of ^{90}Y-Pentixather in the red marrow is even shorter typically not exceeding 2.5 days (d). The residual dose to the red marrow is therefore less than 0.75 Gy 14 d after ^{90}Y-Pentixather treatment with 30 Gy red marrow dose and SCT can be safely administered.

RLT was performed at a median of 4 days (range, 2-23 d) after pre-therapy dosimetry. To reduce renal toxicity, 2L of an amino acid solution containing arginine and lysine (25g/L each) was co-infused in analogy to the joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging practical guidance on receptor radionuclide therapy in neuroendocrine tumors (*22*). Kidney protection by amino acid has been reported to reduce kidney uptake of ^{177}Lu-Pentixather by about 45% (*20*). Vital signs, complete blood count, and blood chemistry were documented during the infusion and within 7 days after administration.

Concomitant Radioimmunotherapy

In 2 patients, radioimmunotherapy (RIT) aiming at CD20 for direct targeting of CD20$^+$ lymphoma cells or CD66 for indirect targeting of bone marrow infiltration was added to enhance anti-lymphoma activity, respectively. For targeting CD20 on DLBCL cells, 15 MBq/kg of ^{90}Y-ibritumomab tiuxetan (Zevalin®, Spectrum Pharmaceuticals, Henderson, Nevada, USA) was infused 7 d after administration of CXCR4-directed RLT, preceded by rituximab 250 mg/m^2 body surface area 1 week prior to as well as on the day of RIT.

In the patient receiving additional RIT targeting CD66 due to high-risk lymphoma with initial bone marrow infiltration (and loss of CD20), the murine anti-CD66 monoclonal antibody BW 250/183 (anti-Granulocyte®, Scintec Diagnostics, Zug, Switzerland) was labelled with ^{188}Re as previously described (*23*) and delivered from the Department of Nuclear Medicine (radiopharmaceutical division) of Dresden

University Hospital. 2 days after ^{90}Y-Pentixather treatment, anti-CD66-targeted RIT with 5.6 GBq (maximum amount available) of ^{188}Re-anti-CD66-BW250/183 was performed. Favorable antibody distribution was verified using whole body planar scintigraphy 44h after RIT.

Conditioning Chemotherapy and Stem Cell Transplantation

All patients except Patient #2 received stem cell grafts from unrelated donors. Therefore, in these subjects additional conditioning chemotherapy included busulfan (in n=5 patients)/ treosulfan (n=1), anti-thymocyte globulin (ATG Fresenius S, Neovii, Rapperswil, Switzerland), fludarabine, and thiotepa. In Patient #5, fludarabine was withheld due to chronic kidney failure.

Safety and Response Assessment

Adverse events were classified as in the Medical Dictionary for Regulatory Activities; severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3; http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ ctcaev3.pdf).

If available (in n=3 patients), response was defined according to Lugano criteria (*24*) after 6, 11 and 16 weeks, respectively. Progression-free survival was defined as the time from RLT until disease progression, initiation of new antitumor therapy, or death.

RESULTS

Patient characteristics

Between November 2015 and February 2017, 6 patients with advanced stage, progressive DLBCL were enrolled. All subjects had been extensively pre-treated and had undergone multiple lines of previous treatment (2-6 lines of treatment, median 3 lines). At time of presentation, multiple lymphoma manifestations in lymph nodes (n=5 patients), bone (n=3), lungs (n=3), kidneys (n=3), pleura (n=2), spleen (n=2), muscle (n=2), adrenal, pancreas, stomach and thyroid (n=1, respectively) were documented.

Pre-therapeutic Dosimetry

The activities of ^{177}Lu-Pentixather administered for the pre-therapeutic dosimetry study and the measured specific absorbed doses in the kidneys, liver spleen, bone marrow, and tumor are listed in Table 2. The kidneys were the dose-limiting organ for all patients (apart from expected myeloablation). Lymphoma doses up to 5.5 Gy/GBq ^{177}Lu-Pentixather (16.7 Gy/GBq ^{90}Y-Pentixather) were deduced.

Therapy and Adverse Events

^{90}Y was administered as the radionuclide of choice in all patients. Due to the shorter half-life of ^{90}Y as compared to ^{177}Lu, the residual dose in the medullary cavities is reliably below 750 mGy after a time interval of 14 days between RLT and subsequent stem cell transplantation (in contrast to a much longer and more heterogeneous interval with ^{177}Lu). The tolerable activity of ^{90}Y-Pentixather was estimated based on the kinetics measured in the pre-therapeutic dosimetry targeting at 23 Gy kidney dose in the 1-ml volume (max_ml) with the highest measured activity concentration. The actually infused activities (2.8 to 6.4 GBq of ^{90}Y), the tolerable activities without kidney protection, and the estimated actually absorbed doses in the kidney max_ml (assuming a 40% kidney dose reduction due to the amino acid solution) are listed in Table 2 for each patient.

During RLT application, no immediate toxic or allergic reactions or changes in vital signs occurred. No acute adverse renal, hepatic or cardiac events were observed.

As expected, RLT (in combination with additional conditioning chemotherapy) resulted in neutropenia <500/µl after a median of 8 d (range, 5-20 d) and complete myeloablation after a median of 13 d (range, 8-23 d) in all patients. Allogeneic SCT was performed after a median of 17.5 d (range, 14-25 d).

Successful engraftment with absolute neutrophil recovery >500 could be observed in 5/6 patients after a median of 11 d (range, 9-13 d). The remaining patient (Patient #3) experienced serious infectious complications during aplasia and died from fungal sepsis 34 d after RLT.

Anti-Lymphoma Activity

Patient #1 died from CNS aspergillosis 29 d after RLT. In the remaining 4/6 patients available for response assessment, partial response was recorded in 2 subjects (Patient #5 and Patient #6; Figure 1) and mixed response in the remaining 2 (Patient #2 and Patient #4). Both patients with partial response had undergone CXCR4-directed RLT in combination with radioimmunotherapy.

Noteworthy, Patient #2 presented with complete remission of all CXCR4-positive lymphoma manifestations but appearance of new receptor-negative lesions (associated to lumbar spinal nerve roots), which were exclusively detected by ^{18}F-fluorodeoxyglucose (FDG)-PET/CT (Figure 2).

During follow-up, another patient (Patient #5) died of pneumogenic sepsis (while being in partial remission), the remaining three (Patients #2, #4, and #6) succumbed to lymphoma progression. Median progression-free survival was 62 d (range, 29-110), median overall survival 76 d (range, 29-334). In total, three patients had died of infectious complications (Patients #1 and #3 during aplasia, Patient #5 after initial successful engraftment 89 days after RLT), the remainder of disease progression.

DISCUSSION

Following initial reports on the feasibility of radioligand therapy with ^{177}Lu- and ^{90}Y-labeled Pentixather in patients with relapsed or refractory multiple myeloma (MM), this is the first description of CXCR4-directed radionuclide therapy in relapsed/refractory DLBCL. In parallel with our previous experience with RLT in MM and acute leukemia (*19*), ^{90}Y-Pentixather as part of the condition regimen prior to allogeneic SCT was well-tolerated and could be readily combined with additional treatment including chemo- or radioimmunotherapy targeting CD20 or CD66. Apart from expected hematotoxicity resulting in myeloablation, no acute renal, hepatic or cardiac adverse events were observed. No toxic or allergic reactions occurred. Due to infectious complications associated with aplasia, two patients died from fungal sepsis 29 and 34 days after RLT, respectively. Transplantation-related mortality was therefore within the reported ranges for allogeneic SCT and was not further increased by additional use of RLT. Successful donor stem cell engraftment could be recorded 10-13 days after transplantation and was not compromised by preceding radionuclide therapy.

Objective partial or at least mixed response could be observed in all patients available for response assessment. Noteworthy, the two patients who underwent additional conditioning radioimmunotherapy were those to achieve partial remission and one might therefore speculate that patients could benefit from even further intensified treatment prior to SCT. However, this very preliminary finding needs to be confirmed in larger trials.

In this small cohort, treatment efficiency correlated with estimated absorbed tumor doses: The two patients with objective response were estimated to achieve highest lymphoma doses of >90 Gy (Patient #5) and >40 Gy (Patient #6), respectively (and additional radioimmunotherapy).

However, response duration was rather short-lived in all cases with median progression-free survival of only 62 days. These results are very comparable to the observations of our pilot studies in MM with initial objective treatment response in more than 80% of cases but disease relapse in all cases after a median of 54 days (*21*). These rather disappointing results might directly reflect patient selection with all

subjects undergoing RLT after exhaustion of all alternative treatments. Given the fact that all patients presented with very advanced, highly refractory lymphoma, more durable responses would have been achieved in earlier disease stages or by adding consolidating or maintaining therapies directly following tumor-debulking CXCR4-directed RLT in order to better address lymphoma heterogeneity and to eradicate surviving DLBCL cell clones. Tumor heterogeneity or clonal evolution could impressively be demonstrated in one patient who presented with complete disappearance of all former, initially CXCR4-expressing lymphoma manifestations but emergence of new, chemokine receptor-negative lesions. While we have recently reported on the dynamic regulation of CXCR4 on the tumor cell surface in response to (bridging) chemotherapy (*25*), the phenomenon of receptor down-regulation of a therapy-resistant sub-clone has not been observed yet. Future basic studies to further investigate and elucidate the underlying pathways are urgently needed. A better understanding of CXCR4 biology might also lead to the identification of synergistic therapy combinations to better address tumor heterogeneity and improve efficacy and duration of CXCR4-directed RLT. Additionally, introduction of α-labelled therapeutic vectors (e.g. ^{213}Bismuth- or ^{225}Actinium-labelled Pentixather) could help to overcome resistance of subclones as recently demonstrated for highly refractory prostate cancer (*26-28*). On short term, new insights will be generated in the COLPRIT trial (Eudra-CT 2015-001817-28), which will focus on the potential role of CXCR4-directed RLT in multiple myeloma and other lymphoproliferative cancers.

This study has several limitations. It is retrospective in design comprising a very limited number of patients. Treatment protocols were not identical in all patients. Due to the obvious need to combine RLT with subsequent stem cell support, the anti-lymphoma efficacy of ^{90}Y-Pentixather as a single agent cannot be reliably assessed.

CONCLUSIONS

In summary, CXCR4-directed RLT as a conditioning regimen in relapsed/refractory lymphoma prior to allogeneic stem cell transplantation is feasible and able to achieve objective responses in even very

advanced disease stages. Given the short response duration, further assessment of this novel treatment earlier in the course of disease and in combination with other treatment approaches to enhance efficacy is needed.

ACKNOWLEDGEMENTS

We thank Gabriele Bohley, Cornelia Schubert, Monika Siemer, Simone Seifert, Michael Schulze-Glück (members of the nuclear medicine team), Inge Grelle and the whole staff of the ward M63 for their support and assistance.

AUTHORSHIP CONTRIBUTIONS

Initials: Constantin Lapa (CL), Heribert Hänscheid (HH), Andreas Schirbel (AS), Malte Kircher (MK), Gerd Wunderlich (GW), Rudolf A. Werner (RAW), Samuel Samnick (SSa), Jörg Kotzerke (JK), Andreas K. Buck (AKB), Hermann Einsele (HE), Hans-Jürgen Wester (HJW), Götz Ulrich Grigoleit (GUG)

Conception and design: CL, HH, MK, AKB, HJW, GUG

Development of methodology: HH, AS, MK, GW, SSa

Acquisition of data: CL, MK, RAW, SSa, GUG

Analysis and interpretation of data: CL, HH, MK, RAW, GUG

Writing, review and/or revision of the manuscript: all authors

Administrative, technical, or material support: HH, AS, GW, SSa, JK, HE, HJW

Supervision: SSa, AKB, JK, HE, HJW, GUG

DISCLOSURE

HJW is founder and shareholder of Scintomics. All other authors declare no conflict of interest.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127:2375-2390.

2. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol.* 2005;23:5027-5033.

3. Kurtova AV, Tamayo AT, Ford RJ, Burger JA. Mantle cell lymphoma cells express high levels of CXCR4, CXCR5, and VLA-4 (CD49d): importance for interactions with the stromal microenvironment and specific targeting. *Blood.* 2009;113:4604-4613.

4. Moreno MJ, Bosch R, Dieguez-Gonzalez R, et al. CXCR4 expression enhances diffuse large B cell lymphoma dissemination and decreases patient survival. *J Pathol.* 2015;235:445-455.

5. Wester HJ, Keller U, Schottelius M, et al. Disclosing the CXCR4 expression in lymphoproliferative diseases by targeted molecular imaging. *Theranostics.* 2015;5:618-630.

6. Chen Z, Teo AE, McCarty N. ROS-induced CXCR4 signaling regulates mantle cell lymphoma (MCL) cell survival and drug resistance in the bone marrow microenvironment via autophagy. *Clin Cancer Res.* 2016;22:187-199.

7. Demmer O, Gourni E, Schumacher U, Kessler H, Wester HJ. PET imaging of CXCR4 receptors in cancer by a new optimized ligand. *Chem Med Chem.* 2011;6:1789-1791.

8. Gourni E, Demmer O, Schottelius M, et al. PET of CXCR4 expression by a (68)Ga-labeled highly specific targeted contrast agent. *J Nucl Med.* 2011;52:1803-1810.

9. Lapa C, Luckerath K, Kleinlein I, et al. (68)Ga-Pentixafor-PET/CT for imaging of chemokine receptor 4 expression in glioblastoma. *Theranostics.* 2016;6:428-434.

10. Lapa C, Luckerath K, Rudelius M, et al. [68Ga]Pentixafor-PET/CT for imaging of chemokine receptor 4 expression in small cell lung cancer--initial experience. *Oncotarget.* 2016;7:9288-9295.

11. Vag T, Gerngross C, Herhaus P, et al. First experience with chemokine receptor CXCR4-targeted PET imaging of patients with solid cancers. *J Nucl Med.* 2016;57:741-746.

12. Philipp-Abbrederis K, Herrmann K, Knop S, et al. In vivo molecular imaging of chemokine receptor CXCR4 expression in patients with advanced multiple myeloma. *EMBO Mol Med.* 2015;7:477-487.

13. Bluemel C, Hahner S, Heinze B, et al. Investigating the chemokine receptor 4 as potential theranostic target in adrenocortical cancer patients. *Clin Nucl Med.* 2017;42:e29-e34.

14. Lapa C, Schreder M, Schirbel A, et al. [(68)Ga]Pentixafor-PET/CT for imaging of chemokine receptor CXCR4 expression in multiple myeloma - comparison to [(18)F]FDG and laboratory values. *Theranostics.* 2017;7:205-212.

15. Werner RA, Weich A, Higuchi T, et al. Imaging of chemokine receptor 4 expression in neuroendocrine tumors - a triple tracer comparative approach. *Theranostics.* 2017;7:1489-1498.

16. Lapa C, Kircher S, Schirbel A, et al. Targeting CXCR4 with [(68)Ga]Pentixafor: a suitable theranostic approach in pleural mesothelioma? *Oncotarget.* 2017;8:96732-96737.

17. Fang HY, Munch NS, Schottelius M, et al. CXCR4 is a potential target for diagnostic PET/CT imaging in Barrett's Dysplasia and Esophageal Adenocarcinoma. *Clin Cancer Res.* 2018;24:1048-1061.

18. Schottelius M, Osl T, Poschenrieder A, et al. [(177)Lu]pentixather: comprehensive preclinical characterization of a first CXCR4-directed endoradiotherapeutic agent. *Theranostics.* 2017;7:2350-2362.

19. Habringer S, Lapa C, Herhaus P, et al. Dual targeting of acute leukemia and supporting niche by CXCR4-directed theranostics. *Theranostics.* 2018;8:369-383.

20. Herrmann K, Schottelius M, Lapa C, et al. First-in-human experience of CXCR4-directed endoradiotherapy with 177Lu- and 90Y-labeled Pentixather in advanced-stage multiple myeloma with extensive intra- and extramedullary disease. *J Nucl Med.* 2016;57:248-251.

21. Lapa C, Herrmann K, Schirbel A, et al. CXCR4-directed endoradiotherapy induces high response rates in extramedullary relapsed Multiple Myeloma. *Theranostics.* 2017;7:1589-1597.

22. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2013;40:800-816.

23. Ringhoffer M, Blumstein N, Neumaier B, et al. 188Re or 90Y-labelled anti-CD66 antibody as part of a dose-reduced conditioning regimen for patients with acute leukaemia or myelodysplastic syndrome over the age of 55: results of a phase I-II study. *Br J Haematol.* 2005;130:604-613.

24. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32:3059-3068.

25. Lapa C, Luckerath K, Kircher S, et al. Potential influence of concomitant chemotherapy on CXCR4 expression in receptor directed endoradiotherapy. *Br J Haematol.* 2018.

26. Sathekge M, Knoesen O, Meckel M, Modiselle M, Vorster M, Marx S. (213)Bi-PSMA-617 targeted alpha-radionuclide therapy in metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017;44:1099-1100.

27. Kratochwil C, Bruchertseifer F, Rathke H, et al. Targeted alpha-therapy of metastatic castration-resistant prostate cancer with (225)Ac-PSMA-617: dosimetry estimate and empiric dose finding. *J Nucl Med.* 2017;58:1624-1631.

28. Kratochwil C, Bruchertseifer F, Rathke H, et al. Targeted alpha-therapy of metastatic castration-resistant prostate cancer with (225)Ac-PSMA-617: swimmer-plot analysis suggests efficacy regarding duration of tumor control. *J Nucl Med.* 2018;59:795-802.

TABLES

	Sex	Age	Disease	Previous lines of therapy	Conditioning regimen	Additional RIT	RLT to neutropenia	SCT to neutrophil reconstitution
1	M	62	DLBCL	2	Fludarabine, busulfan, thiotepa, ATG	No	8	9
2	F	46	DLBCL	3	Fludarabine, busulfan, thiotepa	No	15	10
3	F	64	DLBCL	5	Fludarabine, busulfan, thiotepa, ATG	No	7	n/a
4	M	47	DLBCL	3	Fludarabine, busulfan, thiotepa, ATG	No	7	13
5	F	52	DLBCL	3	Busulfan, thiotepa, ATG	Yes (^{188}Re anti-CD66)	5	13
6	M	55	DLBCL	6	Fludarabine, treosulfan, thiotepa, ATG	Yes (^{90}Y Zevalin®)	20	11

Table 1: Patients´characteristics

RIT = radioimmunotherapy; RLT = radioligand therapy, SCT = stem cell transplantation. All time intervals are given in days.

Patient	#1	#2	#3	#4	#5	#6
Dosimetry *pre-therapy*						
^{177}Lu-Pentixather [MBq]	**224**	**224**	**200**	**208**	**200**	**211**
kidney max_mL [Gy/GBq ^{177}Lu]	**0.8**	**2.9**	**1.3**	**0.8**	***)**	**1.3**
Liver [Gy/GBq ^{177}Lu]	**0.2**	**0.6**	**0.7**	**0.4**	**0.6**	**0.9**
Spleen [Gy/GBq ^{177}Lu]	**0.3**	**0.8**	**0.7**	**1.0**	**1.7**	**0.7**
Bone marrow max_ml [Gy/GBq ^{177}Lu]	****)**	****)**	***)**	**4.8**	**2.4**	**0.9**
Extramedullary lesions max_ml [Gy/GBq ^{177}Lu]	**0.9**	**1.9**	**4.5**		**5.5**	**1.9**
Radioligand therapy (RLT)						
^{90}Y-Pentixather [GBq]	**5.3**	**2.8**	**4.3**	**6.5**	**5.8**	**6.2**
Add. RLT with **^{188}Re anti-CD66 [GBq]**					**5.6**	
Add. RLT with **^{90}Y Zevalin® [GBq]**						**1.4**
Dosimetry *post-therapy (^{90}Y-Pentixather, re-calculated from pre-therapeutic dosimetry)*						
Kidney max_mL (no protection) [Gy/GBq ^{90}Y]	**3.5**	**11.3**	**4.9**	**3.8**	***)**	**5.7**
Liver [Gy/GBq ^{90}Y]	**0.9**	**1.8**	**1.6**	**1.3**	**1.6**	**2.0**
Spleen [Gy/GBq ^{90}Y]	**1.2**	**1.8**	**1.6**	**3.4**	**3.6**	**1.8**
Bone marrow [Gy/GBq ^{90}Y]	****)**	****)**	***)**	**11.4**	**5.1**	**1.9**
Extramedullary lesions max_ml [Gy/GBq ^{90}Y]	**3.9**	**5.3**	**10.4**		**16.7**	**7.1**
kidneys max_mL (with protection*) [Gy]**	**11.2**	**19.2**	**12.9**	**14.6**	***)**	**20.9**
Liver [Gy]	**5.0**	**5.1**	**7.1**	**8.4**	**9.5**	**12.2**
Spleen [Gy]	**6.6**	**5.2**	**7.0**	**21.8**	**20.7**	**11.1**
Bone marrow max_ml [Gy]	****)**	****)**	***)**	**73.8**	**29.4**	**11.7**
Extramedullary lesions max_ml [Gy]	**20.9**	**15.0**	**45.2**		**96.5**	**43.5**

***) Not evaluable because of malignant strcutures. **) No visible Tracer-accumulation. ***) 40% reduction of absorbed radiation dose of the kidneys by co-infusion of an amino acid solution (arginine / lysine)**

Table 2: Overview of administered activities and estimated organ and lymphoma doses

FIGURES and FIGURE LEGENDS

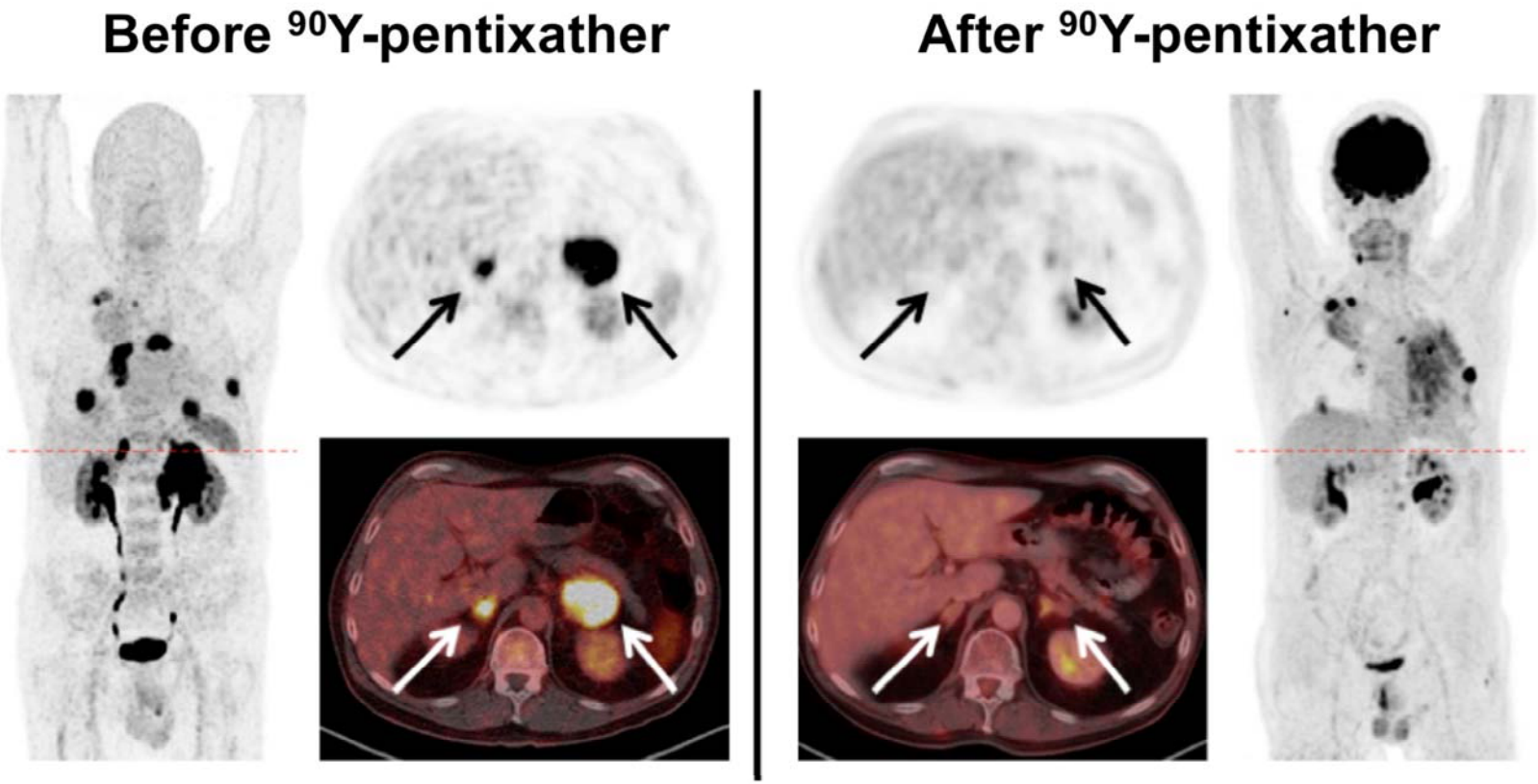

Figure 1: Example of partial response after CXCR4-targeted radioligand therapy (RLT, and additional radioimmunotherapy with ^{90}Y-Zevalin®) as part of conditioning regimen prior to allogeneic stem cell transplantation in DLBCL (patient #6).

Display of maximum intensity projections (outer column) and transaxial slices (inner columns; PET, upper column; PET/CT, lower column) of pre-therapeutic CXCR4-directed and post-therapeutic ^{18}F-FDG-PET/CT. Post-RLT imaging was performed 11 weeks after stem cell transplantation and demonstrated partial response of renal, adrenal (arrows), pulmonary and the majority of nodal DLBCL manifestations. Diffuse left pulmonary tracer accumulation in ^{18}F-FDG-PET were caused by inflammatory changes due to pneumonia.

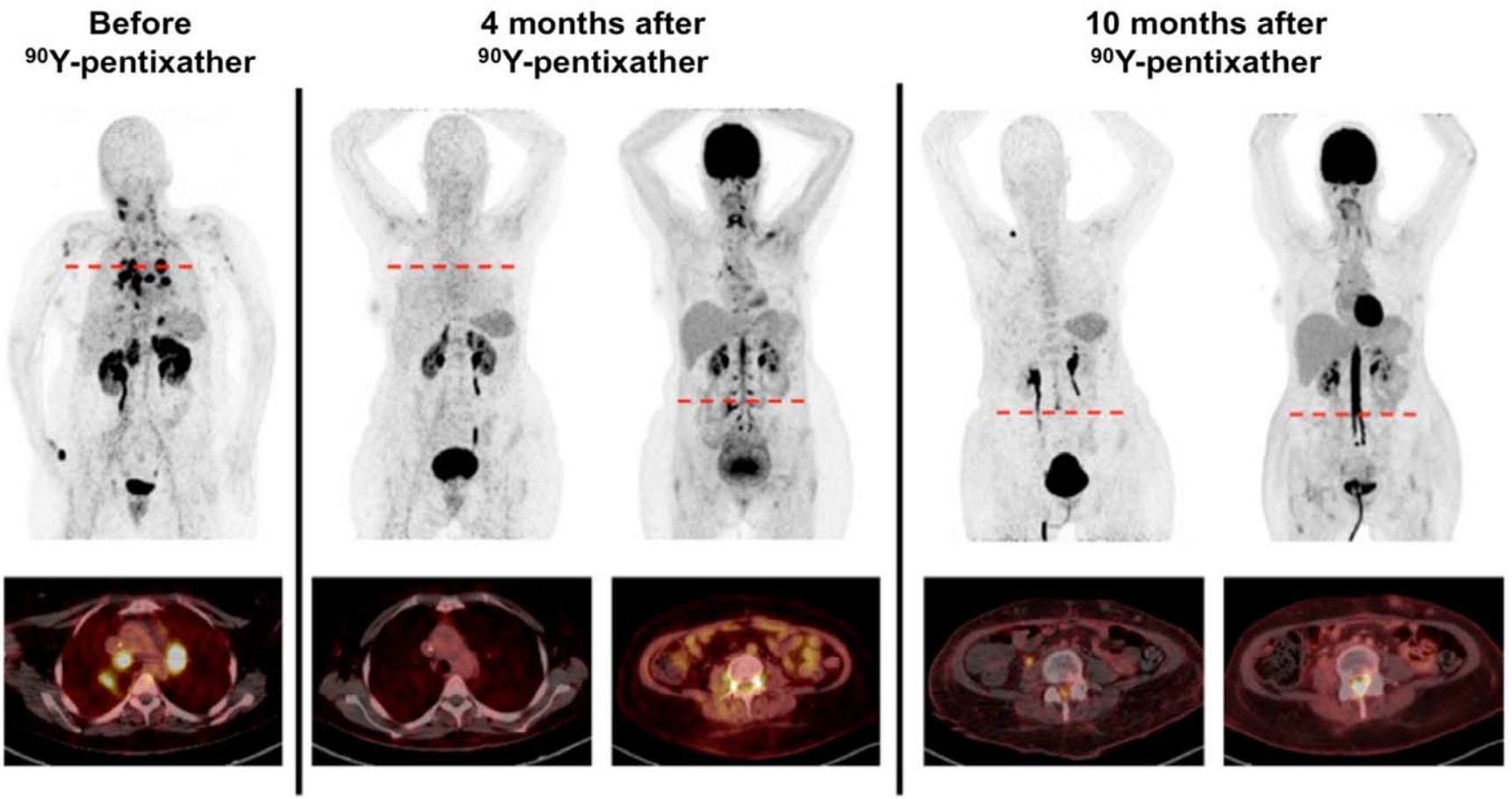

Figure 2: Emergence of viable, CXCR4-negative DLBCL after radioligand therapy (RLT).

Display of maximum intensity projections (MIP) and transaxial fused PET/CT images of patient #2 before, 4 months and 10 months after CXCR4-directed RLT with ^{90}Y-Pentixather, respectively. Whereas RLT resulted in complete remission of all known lymphonodal, pulmonary and adrenal lesions (as compared to pre-therapeutic magnetic resonance imaging), the patient complained about new-onset bladder dysfunction. Additional ^{18}F-

FDG-PET/CT revealed emergence of new viable, CXCR4-negative lymphoma manifestations affecting the spinal cord as well as dorsal root ganglia. Chemotherapy with trofosfamide was started. After initial response, re-staging revealed progressive disease with numerous new paraspinal (still CXCR4-negative) lesions.