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C-X-C Motif Chemokine Receptor 4-Targeted Radioligand Therapy in Patients with Advanced T-Cell Lymphoma

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ABSTRACT

Objectives: C-X-C motif chemokine receptor 4 (CXCR4)-targeted radioligand therapy (RLT) has already been applied to advanced blood cancers, such as multiple myeloma or diffuse large B-cell lymphoma. We herein present a series of patients with advanced T-cell lymphoma (TCL), who were scheduled for CXCR4-directed therapy as conditioning regimen, followed by hematopoietic stem cell transplantation (HSCT). Methods: Four patients with advanced, heavily pretreated and relapsed TCL (2 males, 2 females; median age, 50 years) without suitable alternative therapeutic options underwent CXCR4-directed PET and pretherapeutic dosimetry. We then conducted CXCR4-targeted RLT in combination with allogeneic (3/4, 75%) or autologous (1/4, 25%) HSCT. One patient also underwent radioimmunotherapy targeting CD66 to enhance therapeutic efficacy. We investigated safety, best response, progression-free (PFS) and overall survival. Results: Pretherapeutic dosimetry indicated lymphoma absorbed doses of up to 33.2 Gy from CXCR4-targeted RLT. Except for one patient developing tumor lysis syndrome along with transient grade 3 kidney failure, no acute toxicity, allergic reactions or other adverse events were recorded during therapy. One patient developed septicemia and subsequently died 16 days after RLT, while engraftment was achieved in the remaining 3 subjects (75%). During follow-up, partial response was recorded in 1 patient (33.3%) and complete metabolic response in 2/3 (66.7%, with one patient also receiving additional radioimmunotherapy). Median PFS was 7 months (range, 4 – 25 m). After a median follow-up of 54 m (range, 4 – 56 m), three patients were still alive at date of censoring. Conclusions: For advanced, heavily pretreated TCL, CXCR4-directed RLT may serve as an effective conditioning therapy prior to HSCT and can cause substantial anti-lymphoma activity, leading to remarkable response in selected cases.

Keywords: C-X-C motif chemokine receptor 4, CXCR4, chemokine receptor, theranostics, radioligand therapy, T-cell lymphoma, ^{90}Y/^{177}Lu-PentixaTher, ^{68}Ga-PentixaFor

INTRODUCTION

As an orphan disease, peripheral T-cell lymphoma (TCL) accounts for up to 10% of all non-Hodgkin lymphomas (*1*). The current World Health Organization classification of lymphoid neoplasms listed 29 different subtypes (*2*), while the 5-year survival rate is estimated from 25.4 – 80.2% (*3,4*). First-line treatment consists of CHO(E)P (cyclophosphamide, adriamycin, vincristine, (etoposide) and prednisolone) (*5-7*), while more effective regimens such as brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone can primarily be administered to patients exhibiting CD30+ peripheral TCLs (*8*). In advanced, relapsed or refractory stages, however, therapeutic options are limited and include myeloablative conditioning high-dose chemotherapeutic regimens, followed by hematopoietic stem cell transplantation (HSCT) (*4*).

Recent *ex-vivo* analyses reported on a substantial overexpression of the C-X-C motif chemokine receptor 4 (CXCR4) on human specimen of lymphoma patients (*9*), including peripheral TCL (*10*). Thus, the CXCR4-targeting PET agent ^{68}Ga-PentixaFor has been administered to patients with various subtypes of lymphomas (*11,12*). Such initial reports showed an intense radiotracer accumulation in disease manifestations, in particular for TCL (*11,12*), thereby allowing to identify subjects that can be treated with the therapeutic CXCR4-targeting radiotracer ^{90}Y/^{177}Lu-PentixaTher. Of note, feasibility of treatment with those ß-emitting agents has already been demonstrated, e.g., in patients affected with multiple myeloma, acute leukemia or diffuse large B-cell lymphoma (*13-16*). In the present study, we report on our initial experience of CXCR4-directed radioligand therapy (RLT) as a conditioning therapy for patients with advanced TCL prior to HSCT in a theranostic setting. We also report on anti-lymphoma activity of radiolabeled CXCR4-targeted treatment.

MATERIAL AND METHODS

We offered experimental CXCR4-targeted RLT as conditioning regimen and to achieve anti-lymphoma activity based on the German Pharmaceutical Act (§13.2b). Subjects gave written informed consent for all diagnostic and therapeutic procedures. The local ethical committee of the University Würzburg waived the need for approval as this was a retrospective investigation (# 20220103 01). Subjects have been partly investigated

in (*17*), without assessing the clinical course or achieved doses to tumor or normal organs. Table 1 provides an overview of investigated patients.

CXCR4-directed ^{68}Ga-PentixaFor PET

To assess the retention capacities *in-vivo*, we conducted pretherapeutic CXCR4-directed PET/CT using ^{68}Ga-PentixaFor. This radiotracer was prepared in-house as described previously (*12*). CXCR4 expression was visualized 60 min after i.v. administration of ^{68}Ga-PentixaFor (injected activity, median 136.5 MBq; range, 85 – 157 MBq) using a Biograph mCT 64 or 128 PET/CT system. Expert readers (A.K.B., S.E.S.) confirmed CXCR4 expression in sites of disease (*12*).

CXCR4-directed Dosimetry and RLT

Prior to RLT, all patients underwent dosimetry using ^{177}Lu-PentixaTher (*18*), thereby allowing to provide the exact amount of administrable activity to minimize off-target effects and to calculate the tumor dose at sites of disease. For therapy, we administered 4.8 GBq ^{90}Y-PentixaTher (range, 4.2 – 5.1 GBq; Table 2). Radiotracer synthesis is described in (*14*). Relative to Lu-177 (half-life, 160.8h), the physical half-life of Y-90 is only 64 h and, thus, allows to substantially shorten the time interval until HSCT (*16*). The administrable activity of ^{90}Y-PentixaTher was calculated based on the individual kinetics derived from pretherapeutic dosimetry (with the assumption of a maximum tolerable dose to the kidneys of 23 Gy) (*16*). We then performed RLT 8 days (median value) after pretherapeutic dosimetry (range, 3 – 14 days). As described in (*16*), we also administered a nephroprotective solution consisting of each 25g/L arginine and lysine (overall, 2 L), following a current practical guidance for the execution of receptor targeted radionuclide therapies (*19*). As per our routine protocol, we also assessed vital signs and laboratory values (routine hematology and blood chemistry).

We also conducted a CD66-targeting radioimmunotherapy in one patient (#3), thereby increasing anti-lymphoma effects. Re-188 was attached to murine anti-CD66 monoclonal antibody BW 250/183 (anti-Granulocyte; Scintec Diagnostics) (*16*). Anti-CD66 radioimmunotherapy using 13.5 GBq was then carried out two days after CXCR4 RLT using ^{90}Y-PentixaTher.

Conditioning Chemotherapy/High Dose Therapy and HSCT

3 (75%) patients received allogeneic HSCT, using additional conditioning regimen, while one subject was treated with high-dose therapy followed by autologous HSCT (Supplementary Table 1).

Assessment of Adverse Events and Outcome

We applied the Common Terminology Criteria for Adverse Event version 5.0 (*20*). To assess short-term response to CXCR4-targeted RLT, we measured lactate dehydrogenase (LDH, in U/l) in all patients. A low-dose CT in patient #4, which had been conducted directly prior to conditioning therapy to rule out pulmonary infections, was also investigated to assess a (short-term) anti-lymphoma effect by CXCR4-directed RLT. Image-based best response was determined using current Lugano criteria (*21*). Progression-free survival (PFS) was defined as the time period between initiation of RLT and progressive disease on imaging, or on-set of novel therapy (*16*). Overall survival was determined as initiation of RLT until date of death or alive at date of censoring.

RESULTS

Patient Characteristics

Between November 2015 and December 2021, we included four subjects with relapsed, refractory TCL (2 females, 2 males) with a median age of 50 years (range, 43 – 53 y). Investigated patients had a median of 3 previous treatment lines (range, 2 – 3; Supplementary Table 1). At the time of CXCR4 RLT, multiple manifestations in lymph nodes (n = 4 patients) and bone (n = 2), as well as in kidneys, pleura, spleen, skin, ovary and abdominal bulk (n = 1, each), were recorded.

Pretherapeutic Dosimetry

Respective ^{177}Lu-PentixaTher activities for pretherapeutic dosimetry are shown in Table 2, along with specific absorbed dose to the kidneys, liver, spleen, bone marrow, and tumor (with the kidneys as dose-limiting organs). We expected lymphoma absorbed doses from RLT of up to 33.2 Gy.

CXCR4-targeted RLT and Adverse Events

We administered a median of 4.8 GBq ^{90}Y-PentixaTher. Table 2 shows the estimated absorbed doses to the kidneys (assuming 40% reduction by co-infusion of amino acids). During RLT, vital signs were normal and did not show any alterations in any of the subjects. No acute toxicity, allergic reactions or adverse events were recorded in 3 (75%) patients. In patient #4, however, extensive CXCR4 positive tumor burden caused tumor lysis syndrome with transient grade 3 acute kidney failure two days after RLT (Figure 1). In all patients, CXCR4-directed RLT (and additional radioimmunotherapy in one subject) caused (expected) myeloablation, including neutropenia (<500/µl) 11 days (median) after therapy (range, 11 – 14 days). HSCT was then performed after 14.5 days in all patients (median; range, 14 – 16 days). We observed successful engraftment with an absolute neutrophil recovery in 3 patients, while one patient (#1) died prior to reaching neutrophile reconstitution. Patients #3 and #4 reached engraftment after 12 days, respectively. In Patient #2, however, no immediate successful neutrophile reconstitution after autologous HSCT was recorded, but was achieved after receiving another conditioning therapy and allogeneic HSCT (2 months after CXCR4 RLT, Supplementary Table 1).

Response Assessment

Assessing short-term response, we observed a continuous decrease of LDH right after CXCR4-taregted RLT in patient No. 1 (Figure 2A). For patient No. 2 (Figure 2B) and No. 4 (Figure 2D), a substantial increase of LDH right after CXCR4-targeted RLT was noted, which substantially declined prior to the next therapeutic steps. Further supporting the notion of a substantial anti-lymphoma effect exclusively due to CXCR4-directed RLT, low-dose CT in patient No. 4 (directly prior to conditioning therapy), also demonstrated decrease in lymph node manifestations (Supplementary Figure 1). Patient #1 died due to sepsis caused by diffuse peritonitis 16 days after RLT (without any further available image-based follow-up). Of the 3 subjects available for assessing best response, we observed partial response in 1 patient (#2; 33.3%) and complete metabolic response in 2 patients, respectively (66.7%; #3 and #4).

Further Long-Term Follow-up

Of those 3 subjects available for further long-term follow-up, median PFS was 7 months (range, 4 – 25 m; entire cohort, median 5.5 m). Patient #2 exhibited progressive disease after 7 months and received further regimens of chemotherapy and radiation therapy of inguinal lymph nodes. Patient #3 suffered from progression after 25 months and, thus, donor leukocyte infusion as adoptive immunotherapy was administered. Both patients did not show any signs of progression during further long-term follow-up. For Patient #4, no further follow-up was available after having recorded complete response after 4 months (as date of censoring was reached). All three patients (#2 - 4) were still alive at the time point of censoring (respective median survival, 54 m; range, 4 – 56 m; entire cohort, median overall survival, 29 m).

DISCUSSION

In the present case series, we demonstrated the feasibility of CXCR4-directed RLT in patients with heavily pretreated and relapsed/refractory TCL without suitable treatment options. Except for one patient experiencing tumor lysis syndrome (not life-threating) along with transient grade 3 kidney failure, therapy was well-tolerated, without any acute allergic reactions or toxicity. While one patient died in neutropenia 16 days after RLT, engraftment was achieved in the remaining three subjects (with one subject receiving additional radioimmunotherapy). Of note, those patients demonstrated either partial or complete metabolic response (Figure 1) and were all alive at date of censoring (median survival, 54 months). Thus, our CXCR4-targeting theranostic approach may serve as an effective part of conditioning therapy prior to HSCT and can cause substantial anti-lymphoma activity, leading to remarkable responses in selected cases. Prospective phase I/II studies are now urgently needed to further corroborate our initial findings.

Similar to previous reports, we could not observe any acute adverse events during therapy, except for one tumor lysis syndrome causing a transient and not life-threating grade 3 kidney failure (*17*). However, given the increased CXCR4 expression in hematopoietic stem and progenitor cells within the bone marrow compartment (*22*), CXCR4 therapy led to (desired) cytopenia, while patients are also at increased risk for

infectious disease during follow-up. In our cohort, one patient succumbed to sepsis (caused by Enterococcus faecium and Escherichia coli) 16 days after RLT (patient #1). Such lethal infections, however, are not uncommon in the early post-transplant phase (*23*). In the remaining three subjects, successful engraftment could be achieved, along with remarkable outcome benefits. Of note, in those patients demonstrating complete metabolic response (#3 and #4), no delay in treatment plan occurred and all needed therapeutic steps were performed as scheduled (including CXCR4-directed RLT, complete myeloablation, allogeneic HSCT, and successful engraftment). Patient #2, however, did not reach immediate successful neutrophile reconstitution post-CXCR4 therapy and autologous HSCT and had to undergo another conditioning therapy with consecutive allogeneic HSCT. However, an additional CD66-directed ^{188}Re-radioimmunotherapy may have been used, as previously reported for diffuse large B-cell lymphoma (*16*). As such, in patients with an inadequate response to ^{90}Y-PentixaTher alone, such CD66-targeting radioimmunotherapies or treatment with alpha-emitters (Ac-225) could also be envisioned (*24*).

In lymphoma patients treated with total body irradiation, increasing doses are tightly linked to improved response rates and survival (*25,26*). Such a trend was also observed in the present investigation, e.g., in patient #4 showing a lymphoma dose of up to 33.2 Gy and complete response. This is in line with a previous investigation applying CXCR4-directed RLT for diffuse large B-cell lymphoma, also reporting on doses of 40 Gy in selected cases (*16*). Although the critical renal dose of 23 Gy was not reached in any of our patients, patient #4 developed tumor lysis syndrome along with transient grade 3 kidney failure. Of note, baseline ^{68}Ga-PentixaFor PET had already revealed extensive CXCR4(+) tumor load with a maximum standardized uptake value of up to 38.1 in selected target lesions (Figure 1, PET quantification not shown). Thus, despite all precautions due to pretherapeutic dosimetry, those high-risk individuals with extremely high tumor burden and intense ^{68}Ga-PentixaFor signal should be closely monitored. In this regard, future studies should also elucidate whether PET-based quantification, e.g., of the standardized uptake values or CXCR4-avid tumor volumes may hold potential to identify patients prone to an increased risk of developing relevant off-target effects, including tumor lysis syndrome. Such a quantification of pretherapeutic PETs may also allow to estimate tumor

doses without the need of a time-consuming dosimetry or even to detect patients that most likely benefit from treatment, as recently shown in the context of prostate specific membrane antigen-targeted RLT for prostate cancer (*27*). On the other hand, a recent study did not observe a relevant tumor sink effect in oncological patients scheduled for CXCR4-directed ^{68}Ga-PentixaFor PET (*28*). As such, in patients with advanced disease exhibiting a high tumor load, no decrease of uptake in normal organs was noted, supporting the notion that tumor or normal organ doses may better be calculated from pretherapeutic dosimetry as performed in the present study (*28*).

Our findings have to be interpreted with caution. In our cohort, a substantial overall survival was noted during long-term follow-up, but CXCR4-directed treatment is part of a therapeutic algorithm also including HSCT and, thus, the effects of PentixaTher are difficult to decipher from other concomitant therapies. Nonetheless, we observed either a continuous LDH decline or an increase followed by a rapid decrease of this blood marker right after CXCR4-directed RLT, indicating short term response to PentixaTher. Further ruling out effects of concomitant therapies, patient No. 4 also demonstrated reduction of lymph node manifestations on CT prior to conditioning therapy (Supplementary Figure 1). The retrospective character and small number of patients should trigger future prospective studies. For instance, the COLPRIT phase I/II trial aims to provide further evidence on the impact of the theranostic concept using ^{68}Ga-PentixaFor and ^{177}Lu/^{90}Y-PentixaTher in advanced blood cancers.

CONCLUSION

For relapsed, refractory TCL, CXCR4-directed RLT may serve as an effective part of conditioning regimen prior to HSCT and can cause substantial anti-lymphoma activity, leading to remarkable response in selected cases. This feasibility study demonstrates that further prospective phase I/II studies are needed, which will define the role of implementing CXCR4-directed RLT in the treatment algorithm of TCL patients.

KEY POINTS

QUESTION: Can C-X-C motif chemokine receptor 4-directed radioligand therapy (RLT) exhibit substantial anti-lymphoma activity and serve as a conditioning regimen prior to hematopoietic stem cell therapy (HSCT) in patients with refractory, relapsed T-cell lymphoma?

PERTINENT FINDINGS: While one patient died 16 days after RLT due to sepsis, engraftment was achieved in the remaining three subjects. Those patients demonstrated either partial or complete metabolic response and were all alive at date of censoring with a median survival of 54 months.

IMPLICATIONS FOR PATIENT CARE: Our CXCR4-targeting theranostic approach may serve as an effective conditioning regimen prior to HSCT and can exhibit substantial anti-lymphoma activity, leading to remarkable response in selected cases.

Disclosures:

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REFERENCES

1. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008;26:4124-4130.

2. 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.

3. Timmins MA, Wagner SD, Ahearne MJ. The new biology of PTCL-NOS and AITL: current status and future clinical impact. *Br J Haematol.* 2020;189:54-66.

4. Saleh K, Michot JM, Ribrag V. Updates in the treatment of peripheral T-cell lymphomas. *J Exp Pharmacol.* 2021;13:577-591.

5. Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med.* 2005;352:1197-1205.

6. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328:1002-1006.

7. Schmitz N, Trumper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the german high-grade non-Hodgkin lymphoma study group. *Blood.* 2010;116:3418-3425.

8. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet.* 2019;393:229-240.

9. 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.

10. Weng AP, Shahsafaei A, Dorfman DM. CXCR4/CD184 immunoreactivity in T-cell non-Hodgkin lymphomas with an overall Th1- Th2+ immunophenotype. *Am J Clin Pathol.* 2003;119:424-430.

11. Pan Q, Luo Y, Zhang Y, et al. Preliminary evidence of imaging of chemokine receptor-4-targeted PET/CT with [(68)Ga]pentixafor in non-Hodgkin lymphoma: comparison to [(18)F]FDG. *EJNMMI Res.* 2020;10:89.

12. Buck AK, Haug A, Dreher N, et al. Imaging of C-X-C Motif chemokine receptor 4 expression in 690 patients with solid or hematologic neoplasms using (68)Ga-PentixaFor PET. *J Nucl Med.* 2022. Epub ahead of print.

13. 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.

14. 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.

15. 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.

16. Lapa C, Hanscheid H, Kircher M, et al. Feasibility of CXCR4-directed radioligand therapy in advanced diffuse large B-Cell lymphoma. *J Nucl Med.* 2019;60:60-64.

17. Maurer S, Herhaus P, Lippenmeyer R, et al. Side effects of CXC-Chemokine Receptor 4-directed endoradiotherapy with Pentixather before hematopoietic stem cell transplantation. *J Nucl Med.* 2019;60:1399-1405.

18. Hanscheid H, Schirbel A, Hartrampf P, et al. Biokinetics and dosimetry of 177Lu-Pentixather. *J Nucl Med.* 2022;63:754-760.

19. 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.

20. Common terminology criteria for adverse events (CTCAE)-National cancer institute division of cancer treatment & diagnosis, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60. Accessed 13 March 2022.

21. 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.

22. Karpova D, Ritchey JK, Holt MS, et al. Continuous blockade of CXCR4 results in dramatic mobilization and expansion of hematopoietic stem and progenitor cells. *Blood.* 2017;129:2939-2949.

23. Styczynski J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant.* 2020;55:126-136.

24. McDevitt MR, Scheinberg DA. Ac-225 and her daughters: the many faces of Shiva. *Cell Death Differ.* 2002;9:593-594.

25. Cahu X, Labopin M, Giebel S, et al. Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the acute leukemia working party of EBMT. *Bone Marrow Transplant.* 2016;51:351-357.

26. Hill-Kayser CE, Plastaras JP, Tochner Z, Glatstein E. TBI during BM and SCT: review of the past, discussion of the present and consideration of future directions. *Bone Marrow Transplant.* 2011;46:475-484.

27. Widjaja L, Werner RA, Ross TL, Bengel FM, Derlin T. PSMA expression predicts early biochemical response in patients with metastatic castration-resistant prostate cancer under (177)Lu-PSMA-617 radioligand therapy. *Cancers (Basel).* 2021;13.

28. Serfling SE, Lapa C, Dreher N, et al. Impact of tumor burden on normal organ distribution in patients imaged with CXCR4-targeted [(68)Ga]Ga-PentixaFor PET/CT. *Mol Imaging Biol.* 2022. Epub ahead of print.

TABLES

Patient no.	Sex	Age (y)	Disease	State of Disease before RLT	Additional Radio-immuno-therapy	HSCT	RLT to Neutro-penia (in days)	HSCT to Neutrophile Reconstitution (in days)	Best Response	PFS	OS
1	f	50	T-PLL	PD	No	Allo-geneic	10	NA*	NA*	NA*	16 days
2	m	53	T-Cell Lymphoma (NOS)	PD	No	Auto-logous	11	NA†	PR	7 m	56 m
3	m	50	T-Cell Lymphoma (hepato-splenic/NOS)	PD	Yes (^{188}Re)	Allo-geneic	11	12	CMR	25 m	54 m‡
4	f	43	T-Cell lympho-blastic Lymphoma	PD	No	Allo-geneic	14	12	CMR	4 m‡	4 m‡

Table 1. Patient's Characteristics. Patients #2-4 were alive at last available follow-up. *Patient #1 died after radioligand therapy (RLT) and hematopoietic stem cell transplantation (HSCT), without reaching neutrophile reconstitution. †No immediate successful neutrophile reconstitution after autologous HSCT was recorded, but was reached after following another conditioning therapy and allogeneic HSCT. ‡Complete metabolic response (CMR) at last available follow-up. PFS = progression-free survival. OS = overall survival. T-PLL = T-Cell Prolymphocytic Leukemia. PD = progressive disease. NA = not available. NOS = not otherwise specified. PR = partial response. m = months.

Patient #		1	2	3‡	4
		Pretherapeutic Dosimetry			
Activity (MBq ^{177}Lu-PentixaTher)		200	225	205	210
Specific Absorbed Dose (Gy/GBq ^{177}Lu)	Kidneys	1.1	1.1	0.8	1.6
	Liver	0.5	0.4	0.3	0.5
	Spleen	1.0	0.8	0.3	0.5
	Bone marrow	0.6	0.6	0.4	0.3
	Extramedullary lesion	1.6	1.4		1.9
Kinetics converted to ^{90}Y* (Gy/GBq ^{90}Y)	Kidneys	4.5	4.8	3.7	5.8
	Liver	1.6	1.4	0.9	1.3
	Spleen	2.7	3.3	0.9	1.3
	Bone marrow	1.4	1.5	1.3	1.0
	Extramedullary lesion	4.2	4.6		7.3
		Radioligand Therapy			
Activity (GBq ^{90}Y-PentixaTher)		4.2	4.9	5.1	4.6
Absorbed dose* (Gy)	Kidneys†	11.2	14.0	11.3	15.9
	Liver	6.6	6.6	4.4	5.9
	Spleen	11.2	16.4	4.6	6.2
	Bone marrow	5.6	7.2	6.5	4.8
	Extramedullary lesion	17.4	22.4		33.2

Table 2. Administered Activities, Doses to Organs and Lymphoma. *Estimate based on kinetics of ^{177}Lu-PentixaTher in pretherapeutic dosimetry. †Assumed 40% reduction by co-infusion of amino acids (arginine/lysine). ‡Patient 3 received 13.5 GBq ^{188}Re-anti-CD66 two days after ^{90}Y-PentixaTher.

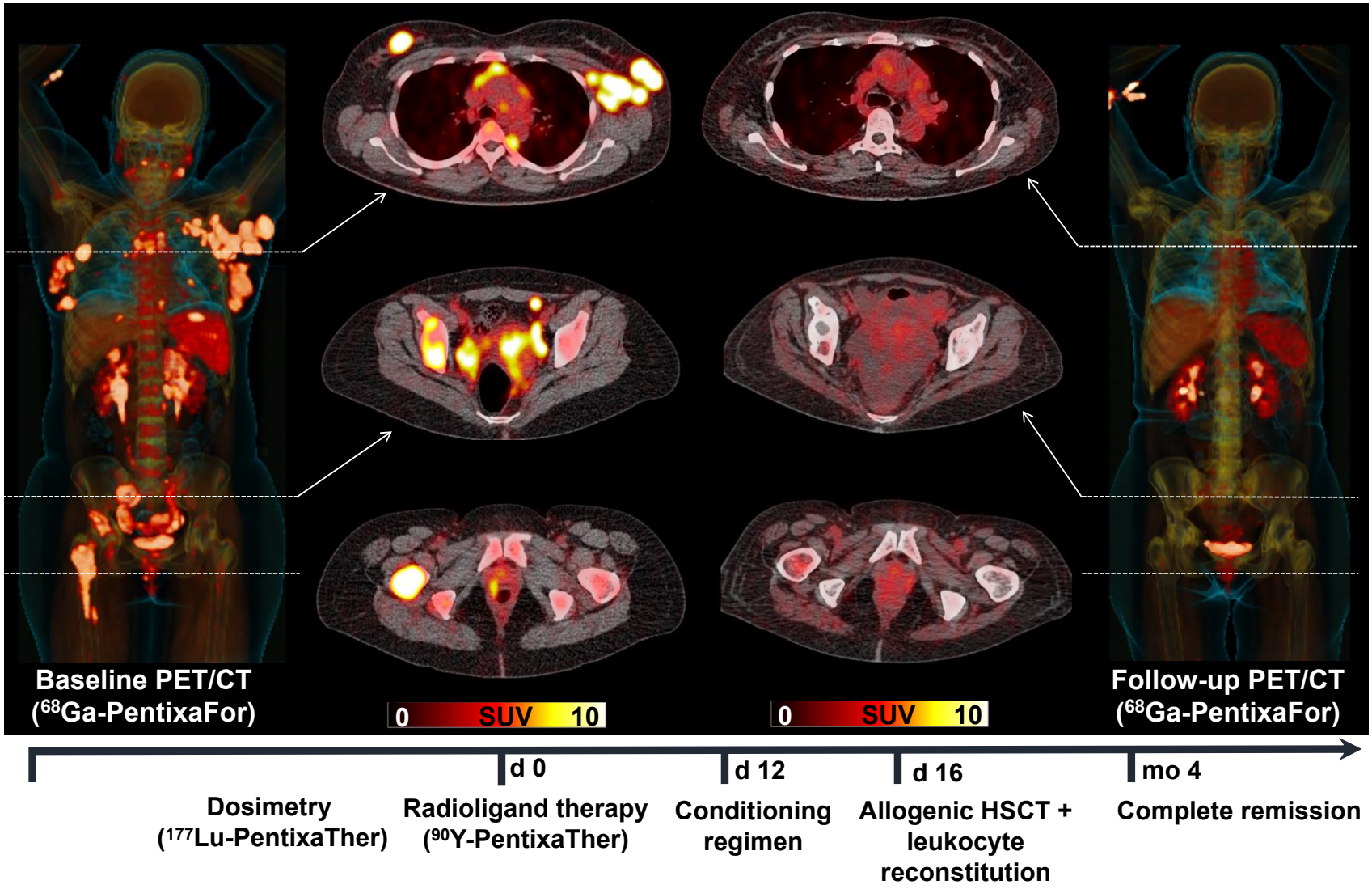


Figure 1. Complete metabolic response after CXCR4-directed radioligand therapy (RLT) as conditioning regimen before allogeneic hematopoietic stem cell therapy (patient no. 4). Maximum intensity projections and transaxial CXCR4-directed

^{68}Ga-PentixaFor PET/CTs prior to (left) and 4 months (mo) after (right) CXCR4-directed RLT using ^{90}Y-PentixaTher. Prior to therapy, patient demonstrated multiple CXCR4 positive sites of disease, including nodal, peritoneal and osseous manifestations, while post-imaging revealed complete response. Time-line of treatment is also displayed. d = days.

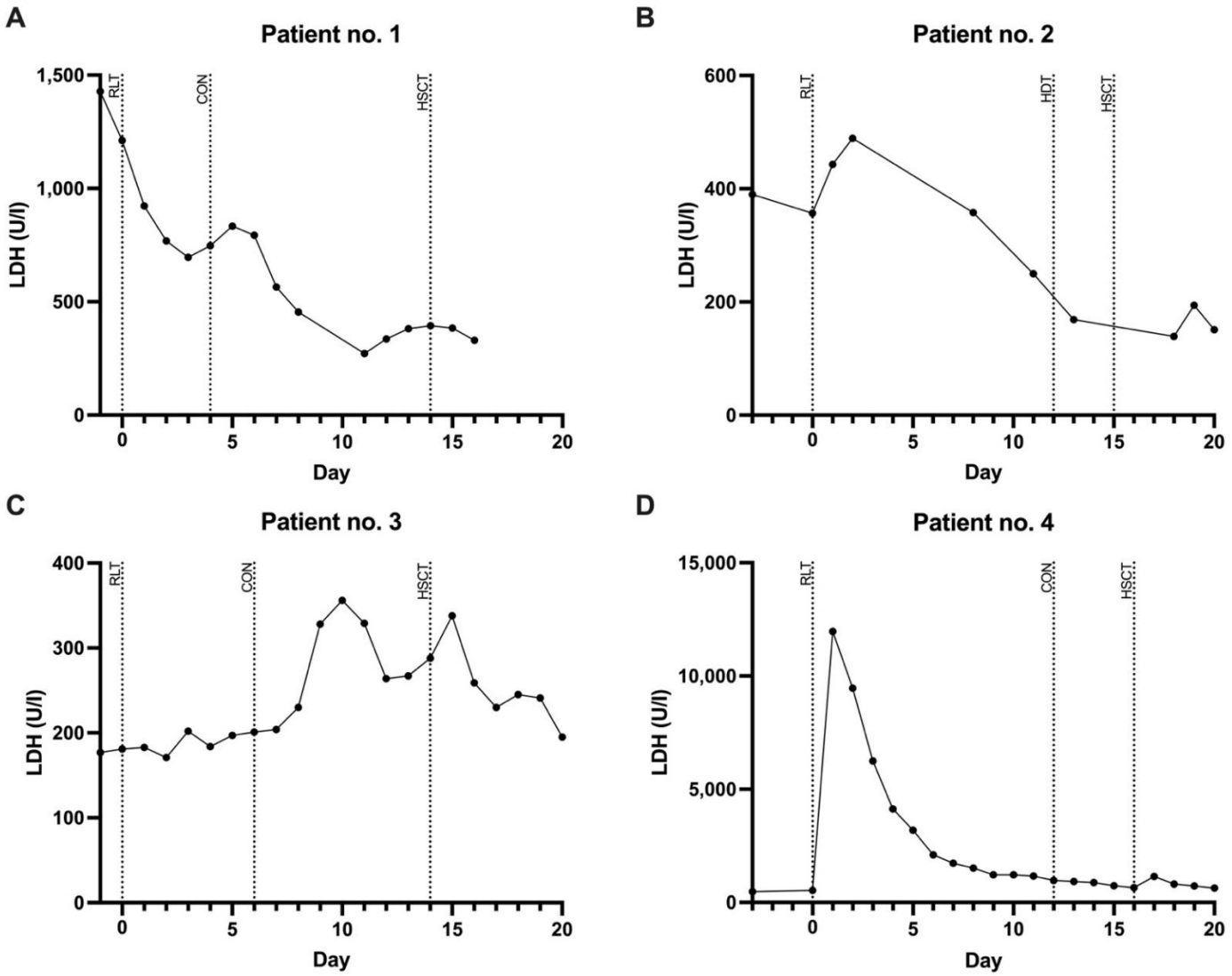


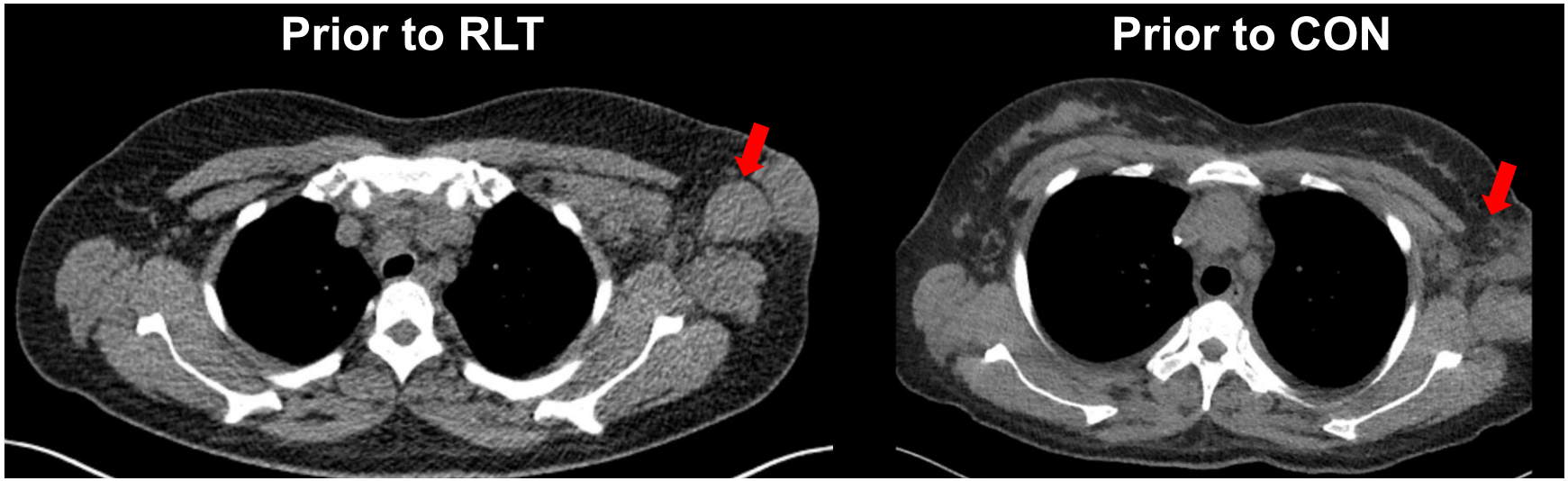
Figure 2. Time-course of lactate dehydrogenase (LDH, in U/l) as an indicator of early response to CXCR4-directed radioligand therapy (RLT). Dotted lines indicate RLT, start of conditioning therapy (CON), high dose therapy (HDT) or

hematopoietic stem cell therapy (HSCT). Patient no. 1 (A) shows a rapid and continuous decline of LDH after CXCR4-RLT. Prior to the next therapeutic steps, patient no. 2 (B) and Patient no. 4 (D) exhibited a remarkable increase of LDH, followed by a massive decline thereafter, supporting the notion of an immediate response to CXCR4-directed RLT in those 3 subjects. Patient no. 3 (C), however, demonstrated modest LDH fluctuations between RLT and CON.

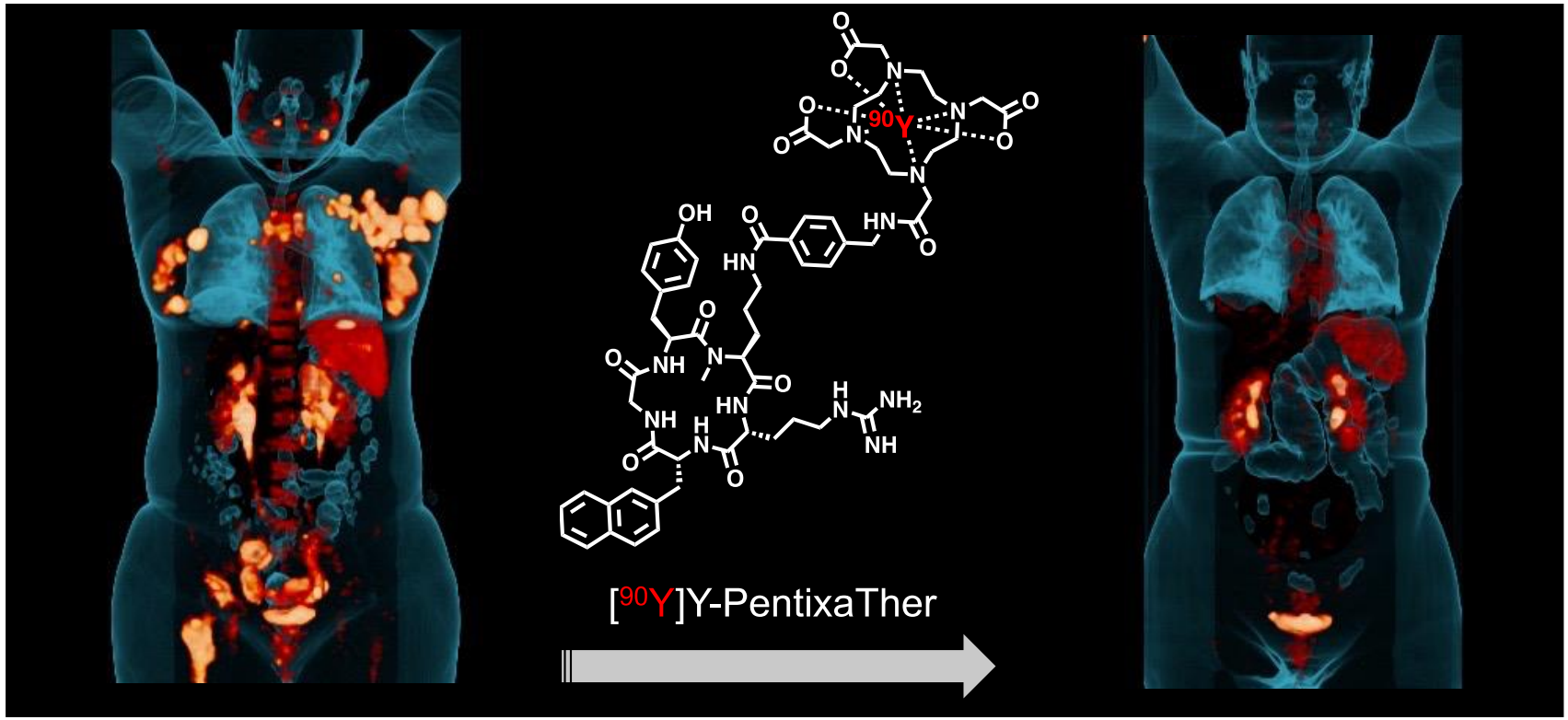
SUPPLEMENTARY MATERIAL

Patient no.	Details on Previous Lines of Therapy	Conditioning or HDT Regimen of Previous HSCT	Drug Doses and Schedule of Conditioning Therapy or HDT Regimen after RLT	RLT to Conditioning Regimen or HDT (in days)	RLT to HSCT (in days)
1	3 lines of therapy - 4 cycles FCM; - 3 cycles Alemtuzumab, allogeneic HSCT; - Alemtuzumab	Fludarabine, Busulfan, ATG	Fludarabine 40mg/m^2 [(d-8) – (d-5)] Melphalan 70mg/m^2 [(d-3) – (d-2)] Thiotepa 5 mg/kg[(d-4)] ATG 10/20/30mg/kg [(d-10) – (d-8)]	4	14
2*	2 lines of therapy - 6 cycles CHOP21; - 2 cycles ESHAP, HD-BEAM, autologous HSCT	BCNU, Cytarabine, Etoposide, Melphalan	Bendamustine 200mg/m^2 [(d-3) – (d-2)]	12	15
3	3 lines of therapy - 4 cycles R-CHOEP; - 1 cycle DHAP; - 3 cycles SMILE	-	Fludarabine 30mg/m^2 [(d-8) – (d-4)] Thiotepa 5mg/kg (d-4) ATG 10/20/30mg/kg [(d-6) – (d-4]	6	14
4	3 lines of therapy - GMALL Protocol; - Nelarabine; - Bendamustine	-	Fludarabine 30mg/m^2 [(d-4) – (d-2)], Busulfan 4 * 0.8mg/kg [(d-4) – (d-3)] ATG 10/20/30mg/kg [(d-4) – (d-2)] Thiotepa 2 * 5mg/kg (d-2)	12	16

Supplementary Table 1. HDT = high dose therapy. HSCT = hematopoietic stem cell transplantation. RLT = radioligand therapy. FCM = Fludarabine, Cyclophosphamide, Mitoxantrone. ATG = Anti-Thymocyte Globulin. CHOP21 = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone. ESHAP = Etoposide, Methylprednisolone, Cytarabine, Cisplatin. HD-BEAM = High-Dose Bis-Chlorethyl-NitrosoUrea (BCNU), Etoposide, Cytarabine, Melphalan. R-CHOEP = Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone. DHAP = Dexamethasone, High Dose Cytarabine, Cisplatin. SMILE = Dexamethasone, Methotrexate, Ifosfamide, L-Asparaginase, Etoposide. GMALL = German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia. *This patient received additional allogeneic HSCT 2 months after CXCR4-targeted RLT and for this procedure, the following conditioning regimen was used: Fludarabine 30mg/m^2 [(d-8) – (d-4)], Busulfan 4 * 0.8mg/kg [(d-6) – (d-5)], ATG 10/20/30mg/kg [(d-4) – (d-2)], Thiotepa 5mg/kg (d-2).



Supplementary Figure 1. Transaxial CT (derived from baseline ^{68}Ga-PentixaFor scan) prior to CXCR4-directed radioligand therapy (RLT, left) and follow-up low-dose CT one day prior to induction of conditioning therapy (CON, right) in patient no. 4. The CT scan on the right was performed as a low-dose CT to rule out pulmonary infection. The axillary lymph node manifestation on the left is no longer visible on follow-up CT (red arrows), indicating an exclusive therapeutic effect of CXCR4-targeted RLT.



Graphical Abstract.