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Research Paper

# Side effects of CXC-chemokine receptor 4 – directed Endoradiotherapy with Pentixather prior to Hematopoietic Stem Cell Transplantation

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**ABSTRACT**

The chemokine receptor CXCR4 is a transmembrane receptor involved in survival, proliferation and dissemination of different cancers, including hematopoietic malignancies. Relapsed/refractory hematopoietic cancers are frequently resistant to conventional therapy and novel highly active strategies are urgently needed. CXCR4-directed endoradiotherapy constitutes a highly promising targeted therapeutic concept. Here we investigated the adverse effects of this novel treatment approach.

**Methods:** Twenty-two patients with heavily pretreated lymphoproliferative or myeloid malignancies were treated with $^{177}$Lu- or $^{90}$Y-Pentixather - a CXCR4-directed therapeutic radioligand - prior to conventional conditioning therapy followed by autologous or allogeneic hematopoietic stem cell transplantation. Twenty-five CXCR4-directed endoradiotherapies were conducted in those patients. Adverse events occurring between endoradiotherapy and the start of conventional conditioning therapy were retrospectively analyzed and graded for the estimation of the safety profile.

**Results:** CXCR4-directed endoradiotherapy with Pentixather showed a favorable toxicity profile. As expected the hematopoietic system was most affected with all subjects developing cytopenias. Except one acute kidney failure grade 3 due to tumor lysis syndrome, overall nephro- and hepatotoxicity was low. Other higher grade adverse events were either transient and resolved, or easily manageable.

**Conclusion:** Therapy with radiolabeled Pentixather appears to be well tolerated and easily applicable when proceeding conventional conditioning regimens for hematopoietic stem cell transplantation.

**Keywords:** Chemokine Receptor CXCR4, Endoradiotherapy, myeloma, lymphoma, leukemia

## INTRODUCTION

Despite substantial advantages in the treatment of hematologic malignancies such as Non-Hodgkin lymphoma, multiple myeloma (MM), and acute myeloid leukemia (AML), those diseases still have high relapse rates and will eventually lead to death in a large proportion of patients (*1,2*). Novel therapeutic strategies targeting the malignant compartment but also the supporting niche are being developed with the goal to specifically reduce tumor cell survival and therapy resistance and consequently improve patient survival.

The CXC-chemokine receptor 4 (CXCR4) with its sole known ligand CXCL12 (also known as SDF-1α) is crucially involved in multiple physiological functions, such as cell growth, survival and migration. In the hematopoietic system CXCR4 plays a critical role in immune cell trafficking and the retention of hematopoietic stem/progenitor cells (HSPC) within their bone marrow (BM) niche. Cancer cells have been shown to hijack the physiological functions of CXCR4, and, consequently, CXCR4 overexpression has frequently been associated with a dismal prognosis (*3-5*). In particular in hematologic cancers CXCR4 is crucially involved in the crosstalk between the malignant cells and their supporting niche. Therefore, the CXCL12/CXCR4 axis is considered a highly promising target for therapy.

Due to the successful development of a radiolabeled CXCR4 ligand ($^{68}$Ga-Pentixafor) it is now possible to visualize CXCR4 expression in vivo by means of positron emission tomography (PET) imaging (*6,7*). Several proof of concept studies have shown the potential of the PET-tracer $^{68}$Ga-Pentixafor to visualize CXCR4 positive tumors with a specific applicability for patients with hematologic diseases such as Non-Hodgkin lymphoma (*8*), MM (*9,10*) and acute leukemia (*11*).

A theranostic approach by combining CXCR4-directed imaging to select patients for CXCR4-directed endoradiotherapy is enabled by the peptide Pentixather. Pentixather is a modified structure of the CXCR4-directed tracer peptide Pentixafor, which allows the linkage of β-emitting radionuclides ($^{177}$Lutetium ($^{177}$Lu); $^{90}$Yttrium, ($^{90}$Y)) routinely used in clinical practice for various cancer radiotherapies (*12-14*). $^{177}$Lu-Pentixather has already been proven to successfully eradicate CXCR4-positive tumor cells without completely and irreversibly destroying the supporting HSPC niche in a preclinical endoradiotherapy mouse model, which is a prerequisite for the reconstitution of the hematopoietic system after therapy. Moreover, first-in-human experiences of CXCR4-directed endoradiotherapy with Pentixather in patients with advanced-stage MM, AML and Non-Hodgkin lymphoma have shown the feasibility of this

therapy in combination with high-dose chemotherapy and autologous or allogeneic hematopoietic stem cell transplantation (HSCT) (*10,15-17*). However, due to the high expression levels of CXCR4 on HSPCs and its crucial function in their regulation, the safety of CXCR4-directed endoradiotherapy has to be further studied.

Here, we report on the toxicity profile of CXCR4-directed endoradiotherapy with $^{177}$Lu- and $^{90}$Y-Pentixather. For this retrospective analysis we analyzed data from 25 CXCR4-directed therapies with Pentixather that were conducted within individual therapy approaches on compassionate use basis in 22 patients. By reporting the side effects of this therapy in a substantial patient group, this investigation provides crucial information for the design and implementation of future prospective clinical studies.

## PATIENTS AND METHODS

### Patients

Twenty-two patients with advanced lymphoproliferative and myeloid cancers were treated and studied from 2014 to 2016 at the University Hospital Würzburg. All patients were heavily pretreated with no option for further standard therapies. Detailed description of the two patients receiving repeated Pentixather treatments are provided in the Supplemental Material.

Given the lack of alternative treatment options, and in view of the documented CXCR4 expression (confirmed *in vivo* by means of $^{68}$Ga-Pentixafor PET imaging) and availability of a HSCT donor or an autologous graft, an interdisciplinary board of specialists opted for CXCR4-targeted endoradiotherapy combined with high-dose conditioning chemotherapy and autologous or allogeneic HSCT. The decision on combination of Pentixather with a second radiopharmaceutical was based upon patient and disease characteristics and the type of transplantation and subsequently performed as suggested within the interdisciplinary board. The clinical ethics committee of the University Hospital Würzburg (responsible internal review board) approved individual treatments on a compassionate-use basis (German Drug Act, §13,2b). All subjects gave written informed consent before receiving the therapy.

Treatment related data of some patients have been previously described in feasibility studies of CXCR4-directed endoradiotherapy with Pentixather (*15-17*). Those data have thus not been analyzed in a structured retrospective manner heretofore.

### Dosimetry

The dosage of activity for endoradiotherapy was based on the result of a pre-therapeutic dosimetry study with a tracer activity of $^{177}$Lu-Pentixather in each patient. Detailed information about the pre-therapeutic dosimetry study is provided within the Supplemental Material.

In patients treated with $^{177}$Lu-Pentixather, the measurements described in the Supplemental Material were repeated with reduced acquisition durations in order to assess the actually absorbed doses. Due to the inherent problems and uncertainties of dose determination with pure β-emitters, no dosimetry was performed after administration of $^{90}$Y. Therapeutic absorbed doses per unit activity of $^{90}$Y-Pentixather were estimated by recalculating the bi-exponential decay functions measured with $^{177}$Lu in the tracer study to the shorter half-life of the $^{90}$Y.

**Therapy**

The administered endoradiotherapy activities for myeloablation were chosen to target at 23 Gy maximum absorbed dose to the kidneys. The specific absorbed dose determined from the tracer study for the 1 ml volume with the highest activity concentration within the kidneys was used to calculate the required activity. In order to reduce trapping of peptides in renal tubules and thus toxicity, amino acid solution (25 g L-arginine and 25 g L-lysine diluted in two liter of normal saline) was co-infused for myeloablative therapy as recommended for peptide receptor radionuclide therapy (*18*).

**Assessment of Adverse Events**

Vital signs, complete blood count and serum chemistry including values corresponding to the kidney and liver function as well as electrolytes were documented from the day of the infusion of the radionuclide on a daily routine. In addition to the lab work analysis a clinical assessment (gastro-intestinal, cardiac, renal, pulmonic and nervous system, examination of the skin and possible signs of infection) was performed on a daily basis according to the standards of the transplant unit. Adverse events (AEs) that occurred from the day of the radionuclide infusion to the day of the start of the conventional conditioning regimen were included into the retrospective analysis. AEs occurring after the beginning of the conditioning regimens were considered to be due to chemotherapy and the transplantation itself and were not included in this analysis.

All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

## RESULTS

### Patient Characteristics

In total 25 CXCR4-directed endoradiotherapies with Pentixather were conducted in 22 patients with advanced blood cancers prior to conventional conditioning therapy followed by autologous or allogeneic HSCT. The median age was 54 years with a range from 31 to 68 years. Most patients presented with MM (10 patients), diffuse large B-cell lymphoma (6 patients) and AML (4 patients). One patient each had the diagnosis of mantle cell lymphoma and T-cell prolymphocytic leukemia. All patients were heavily pretreated, having received at least two standard therapy regimens and a median number of four previous therapy lines (standard or experimental). Over 80% of the patients had a previous autologous or allogeneic HSCT. Detailed patient characteristics are displayed in Table 1.

### Dosimetry and Treatment Characteristics

Activities of 206 ± 10 MBq of $^{177}$Lu-Pentixather were administered for pre-therapeutic dosimetry. The kidneys were the dose-limiting organ for all patients receiving treatment for myeloablative therapy. Activity kinetics in the kidneys was generally bi-exponential with a negative short-lived component, indicating further accumulation early after the activity administration, and a dominant long-lived component. The effective half-life of the dominant component was 37 ± 12 hours with one outlier at 97 hours, which is slightly shorter than typically observed in octreotide endoradiotherapy (*19-21*). The renal absorbed dose per unit administered activity was 1.6 ± 0.7 Gy/GBq $^{177}$Lu-Pentixather without nephroprotection, which is slightly higher than in octreotide endoradiotherapy (*22*). The nephroprotective medication reduced the therapeutic maximum kidney dose per administered activity in the six patients treated with $^{177}$Lu-Pentixather to 64% ± 13% of the values measured in pre-therapeutic dosimetry. Recalculation of the kidney doses for the therapy with $^{90}$Y-Pentixather with protective medication resulted in 4.0 ± 1.7 Gy/GBq. Slight mean decreases in specific absorbed doses during therapy were also observed for the liver (86% ± 15%), the spleen (88% ± 8%), and in extramedullary lesions (82% ± 30%) in the patients treated with $^{177}$Lu-Pentixather (see Supplemental Table S1 for details). In these patients, mean effective half-life of the therapeutic activity in the bone marrow was 115 ± 14 h; the expected effective half-life for $^{90}$Y in the marrow would have been 55 ± 3 h. A representative pre-therapeutic PET-

CT with $^{68}$Ga-Pentixafor, as well as the dosimetry data from one patient with an extramedullary AML are shown in Fig. 1.

According to the pre-therapeutic dosimetry and with a maximum tolerated kidney dose of 23 Gy, patients were treated for myeloablation by intravenous infusion of 7.6 to 23.5 GBq of $^{177}$Lu-Pentixather (6 therapies) or 2.4 to 8.4 GBq of $^{90}$Y-Pentixather (19 therapies). CXCR4-directed endoradiotherapy with $^{90}$Y-Pentixather was further combined with $^{188}$Re-CD66 in six patients and $^{90}$Y-Zevalin and $^{153}$Sa-EDTMP in one patient each (Table 2 and Supplemental Table 2). The expected kidney doses from the additional therapies were taken into account in the dosage of Pentixather. The actually administered doses from therapy with Pentixather in the milliliter with the highest activity concentration in the kidneys were measured to be 13.0 ± 1.9 Gy (range: 10.5 – 16.0 Gy) after $^{177}$Lu and, taking the protective medication during therapy into account, estimated to be 16.4 ± 3.6 Gy (range: 11.2 – 22.2 Gy) after $^{90}$Y.

**Adverse Events**

A total of 340 AEs were detected after the 25 conducted Pentixather treatment courses. Among those, 86 events (25.3%) showed a severity of grade 3 or higher. One patient developed acute tumor lysis syndrome with acute kidney failure grade 3 that led to discontinuation of the further treatment plan (Table 3). The therapy regimen (endoradiotherapy, conditioning chemotherapy, HSCT) could be finished as intended in all the other 24 conducted CXCR4-directed treatment courses.

The most common AEs were expectedly seen in the hematopoietic system. During all treatment courses patients developed anemia, after 17 of 25 courses bearing grade 3 or grade 4 toxicity. All patients developed neutropenia and thrombocytopenia respectively. Grade 3 or 4 toxicities concerning neutropenia and thrombocytopenia occurred in at least 20 of 25 treatment courses, irrespective of the administered radionuclide – $^{177}$Lu or $^{90}$Y respectively (Table 4, Supplemental Table 3 and Fig. 2).

Sites of elimination and excretion of the radiopharmacon include kidney and liver. Thus, the impact on renal and hepatic function was of special interest. Notably, only during 2 of 25 treatment courses patients presented with acute kidney failure. During one treatment course a patient developed grade 3 kidney failure in the context of tumor lysis syndrome mentioned above. In 58% of the treatment courses we observed an elevation of transaminases and in 23% bilirubin levels increased. Importantly,

those changes were not severe (grade 1-2) and there was no higher-grade toxicity or limitation of the hepatic synthesis activity (e.g. disruption of plasmatic coagulation) (Supplemental Table 4 and Table 4).

Fitting the high percentage of neutropenia after application of the radiopeptide, and as expected in such a heavily pretreated patient cohort with hematopoietic cancers, a substantial rate of infections, including grade 3 or grade 4 infections (sepsis) occurred after 9 of the 25 conducted treatment courses (36%). Notably, all of these patients recovered after admission of preemptive or targeted antibiotic treatment and could proceed to the conditioning chemotherapy and HSCT (Supplemental Table 5).

Other AEs, such as electrolyte disorders (Suplemental Table 6), gastrointestinal toxicities (Supplemental Table 7), cardiovascular side effects (Supplemental Table 8), toxicities of the nervous system (Supplemental Table 9) or general disorders (Supplemental Table 10) were in general self-limiting or manageable without delay of further therapy.

**Characteristics of Further Therapy**

After treatment with Pentixather, all but one patient underwent subsequent conditioning/high-dose chemotherapy with either autologous or allogeneic HSCT (Table 5). As stated above, treatment with $^{177}$Lu-Pentixather as well as $^{90}$Y-Pentixather led to grade 3 or grade 4 cytopenias and thereby to the assumptive reduction of tumor cell burden in the hematopoietic niche (Table 4, Supplemental Table 2 and Fig. 2).

Conventional chemotherapy and subsequent HSCT was first started when radiation was decayed, as the transplanted HSPCs should not be exposed to radiation-associated toxicity. It was therefore not unexpected due to the shorter half-life of $^{90}$Y (2.7 days as compared to 6.7 days for $^{177}$Lu), that the median time from CXCR4-directed endoradiotherapy to the beginning of conventional conditioning therapy was significantly shorter in patients who received $^{90}$Y-Pentixather compared to $^{177}$Lu-Pentixather (Fig. 3).

Engraftment of HSPC, defined by leukocyte and platelet engraftment, was not impaired by endoradiotherapy with Pentixather. Leukocyte engraftment occurred on day 11.4 (mean, range 9-14) after autologous and on day 12.2 (mean, range 10-20) after allogeneic HSCT. On day 14 (mean, range 9-18) after autologous and on day 13.25 (mean, range 10-16) after allogeneic HSCT platelet engraftment was reached (Table 5). Due to the heavily pretreated patient collective, often with active disease and poor general condition, ten patients died before complete engraftment due to neutropenic sepsis or tumor progression.

**DISCUSSION**

The toxicity profile obtained from this retrospective analysis clearly demonstrates the feasibility of CXCR4-directed endoradiotherapy with Pentixather when combined with conventional conditioning regimens. Due to the high rates of hematologic toxicities, we currently assume that this therapy can only successfully be applied embedded in a HSCT concept.

Owing to the relatively high CXCR4 expression within the HSPC compartment, the most severe adverse effects could be attributed to the hematopoietic system with approximately 70% of higher grade AEs involving cytopenias. Apart from one patient who developed tumor lysis syndrome that subsequently led to discontinuation of therapy, no further death could directly be attributed to endoradiotherapy. It is important to consider that hematotoxicity could reflect a sufficient eradication of the HSPC compartment, which should be studied in subsequent trials by BM biopsies after endoradiotherapy and before further conditioning.

Higher doses of total body irradiation prior to HSCT go along with superior remission rates. However, due to the severe non-hematologic side effects of unselective irradiation that often leads to an unacceptable rate of treatment related mortality, those conditioning regimens are restricted to young and healthy patients (*23*). CXCR4-directed endoradiotherapy might have the potential to circumvent the non-hematologic side effects of total body irradiation and therefore translate the high remission rate attributed to radiation into an increased rate of OS. Furthermore, such endoradiotherapy provides the possibility to be used after previous conditioning with total body irradiation.

Although the eradication of the tumor-supporting niche, caused by crossfire effects when using β-emitters, is presumed a major point of action in CXCR4-directed endoradiotherapy, destruction of the stem cell niche could bear an incalculable potential risk. An impaired support of the transplanted HSPCs may lead to engraftment failure and long lasting cytopenias that have been associated with high mortality rates (*24*). Recent work in a preclinical mouse model however showed that mesenchymal stem cells, or stromal cells, an important component of the BM stem cell niche, preserve their ability to support HSPCs after CXCR4-directed endoradiotherapy with $^{177}$Lu-Pentixather (*16*). Those observations are mirrored by the unimpaired leukocyte and platelet engraftment after therapy with both $^{90}$Y- and $^{177}$Lu-labelled Pentixather and subsequent HSCT in the herein studied patient population that compared well to mean leukocyte engraftment of 16.4 days and mean platelet engraftment of 13 days after allogeneic HSCT. (25).

Due to tracer elimination through the liver and most importantly through renal excretion, toxicity to these organs limits the maximal administered activity of radionuclide-conjugated Pentixather. The activity dosage in our patients was conservative insofar as no kidney protection medication was administered in the tracer study and the limit of 23 Gy was not applied to the mean kidney dose but to the 1 ml partial volume with the maximum activity concentration. Therefore it is of great significance that this retrospective analysis revealed no grade 3 or higher acute liver toxicity in the 25 conducted endoradiotherapy courses. The one case of acute kidney failure occurred in a patient with tumor lysis syndrome. The specific absorbed dose in the 1 ml volume with the highest activity concentration in the kidneys was determined from the tracer study to be 7.0 Gy/GBq 90Y-Pentixather; the patient received 2.62 GBq corresponding to an estimated dose of 18.3 Gy. It is speculative that the observed endoradiotherapy-mediated tumor lysis in combination with acute radiation-associated toxicity contributed to the further clinical course.

Apart of liver and renal toxicity most other AEs were transient in nature and self-limiting without further intervention, except for the high rates of infections observed after endoradiotherapy. These are most likely attributed to the high rates of leuko- and neutropenia and were usually manageable with antibiotic treatment. Importantly, these infectious complications underscore the importance to aim for a short period of neutropenia and a short interval to conventional conditioning and HSCT, as septic events during this time are frequent causes of treatment-related mortality in the setting of HSCT (*26*). Very importantly, this analysis disclosed a significantly and clinically relevant shorter time interval between endoradiotherapy and beginning of the conventional conditioning therapy when using $^{90}$Y-Pentixather as compared to $^{177}$Lu-Pentixather.

Within this analysis, we purposely chose to limit the report of side effects to the interval between endoradiotherapy and start of conventional therapy to get an initial impression of acute side effects of CXCR4-directed endoradiotherapy. Therefore, no definitive conclusion can be drawn on long-term toxicities of CXCR4-directed endoradiotherapy with Pentixather, or on additive or synergistic effects in the combination with conventional therapies. Studies on other radiolabeled peptides, such as $^{177}$Lu-Dotatate, have shown a slightly increased risk of peptide receptor radionuclide therapy for the development of myelodysplastic syndromes or AML (*13,27*). These long-term toxicities concerning the hematopoietic

system are most probably caused by radiation-associated toxicity on the HSPCs. Such toxicities might however be bypassed by the integration of CXCR4-directed endoradiotherapy in a HSCT concept.

Although this retrospective analysis in a substantial number of patients provides a fairly detailed toxicity profile for CXCR4-directed endoradiotherapy and demonstrates its feasibility and points to putative effectiveness of this therapy, there are evident limitations. First, due to the retrospective analysis of the data, some toxicity data of clinical relevance could have been missed due the lack of prospective, coordinated data collection as obtained within a controlled study. Second, the patient collective described is very heterogeneous and previous therapies as well as conditioning regimens have not been consistent. Moreover, some of the observed toxicities might be caused by the administration of other radionuclide-conjugated vectors, such as $^{188}$Re-CD66, $^{90}$Y-Zevalin and $^{153}$Sa-EDTMP. A prospective clinical phase I/II trial is therefore urgently needed to clearly determine the toxicity as well as the effectiveness of CXCR4-directed endoradiotherapy with Pentixather and will be conducted in the COLPRIT trial (Eudra-CT 2015-001817-28).

**CONCLUSION**

CXCR4-directed endoradiotherapy with Pentixather could be a safe and easily applicable way to further enhance the anti-tumor effect of high-dose chemotherapy and conditioning regimens in combination with HSCT, and to target the stem cell niche. With a side effect profile pointing towards grade 3-4 AEs within the hematopoietic compartment, where tumor burden was high and where this effect is anticipated and desirable, the use of radiolabeled Pentixather represents a promising treatment option in heavily pretreated patients with advanced lymphoproliferative and myeloid CXCR4-positive cancers. Further investigations regarding safety and efficacy should be performed in the context of prospective phase I/II studies.

## AUTHOR CONTRIBUTIONS

S.M., P.H., R.L. and H.H. collected data. S.M., P.H., R.L., H.H., A.S., M.K., C.M., U.K. and C.L. analyzed and interpreted the data. U.K., G.-U.G. and C.L. designed the retrospective analysis. A.B., H.-J.W. and H.E. provided critical input. S.M. P.H., H.H., U.K. and C.L. wrote the manuscript. All authors critically reviewed and approved the final manuscript.

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## COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: All authors declare no conflict of interest.

Research involving human participants: The data in this study represent a retrospective analysis of therapies and not a prospective clinical trial. Studies and analyses were performed in accordance with the ethical standards of the institutional research committee.

Informed consent: Written informed consent to the clinical treatment and to data analysis was obtained prior therapy from all patients.

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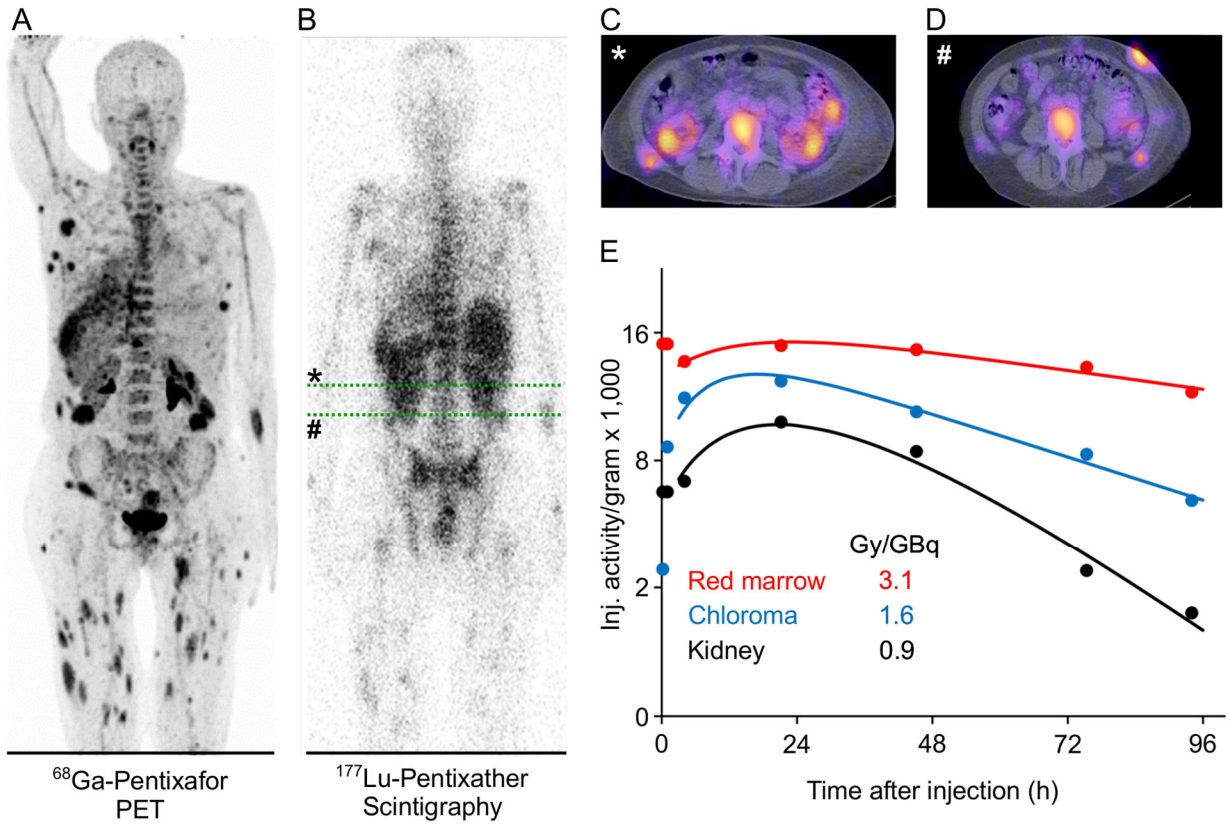


**Figure 1. Pre-therapeutic $^{68}$Ga-Pentixafor PET and dosimetry with $^{177}$Lu-Pentixather in a representative patient with extramedullary AML.**

A) Maximum intensity projection of $^{68}$Ga-Pentixafor PET (89 MBq of $^{68}$Ga-Pentixafor, acquisition 1h after injection) and B) planar whole-body scintigraphy (204 MBq of $^{177}$Lu-Pentixather, acquisition 2 days after injection) demonstrating concordant tracer accumulation in BM as well as multiple extramedullary AML lesions. C+D) Sufficient CXCR4 expression can also be determined in transaxial SPECT/CT (representative images of the abdomen [green lines in B)]. E) Time-activity curves (up to 96 h after injection) demonstrating highest achievable dose per injected activity for the red marrow.

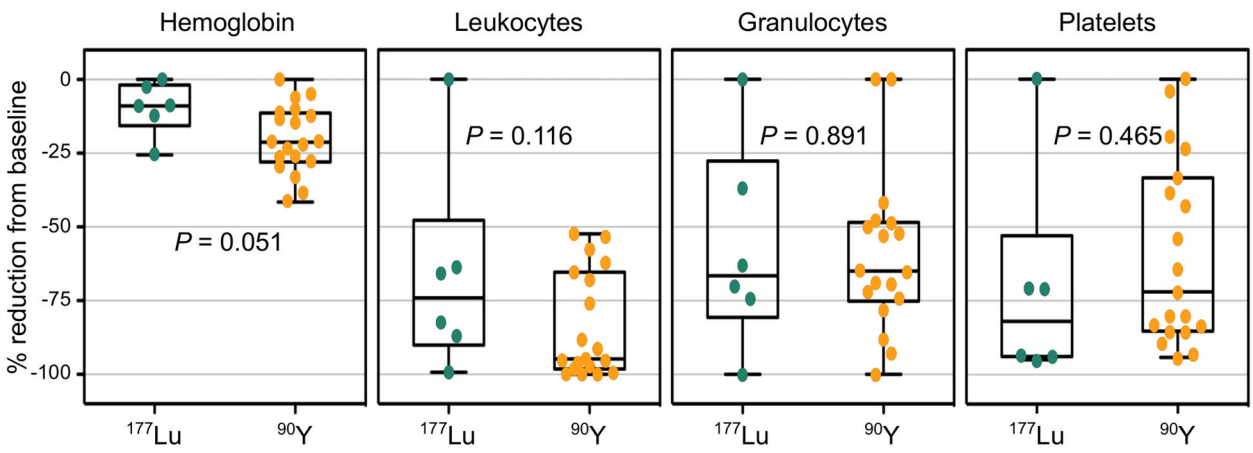


**Figure 2. Cytopenias relative to baseline after CXCR4-directed** endoradiotherapy**.**

Depicted is the reduction of hemoglobin, leukocyte, granulocyte and platelet values in % from baseline after respective Pentixather therapy ($^{177}$Lu or $^{90}$Y) before start of conventional conditioning therapy. Each dot represents the value of one conducted therapy. Shown are box-whiskers blots, *P* - value calculated using t-test.

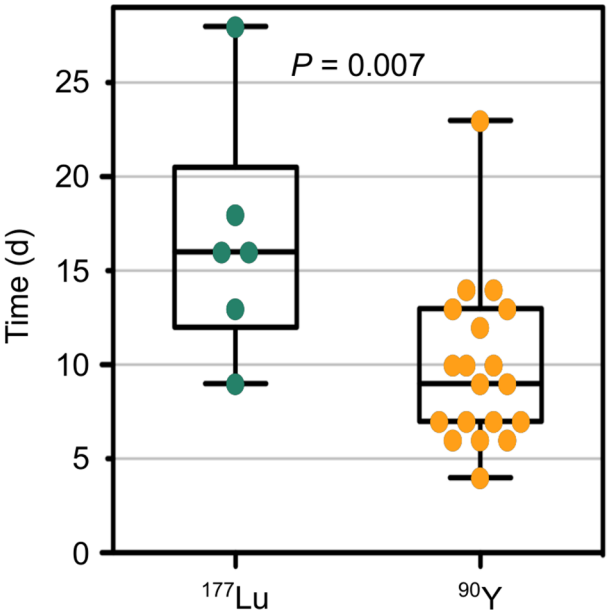


**Figure 3. Interval between CXCR4- directed** endoradiotherapy **and start of conventional conditioning therapy.**

Depicted are the days between application of either $^{177}$Lu-Pentixather or $^{90}$Y-Pentixather (half-life $^{177}$Lu vs. $^{90}$Y: 6.7 vs. 2.7 days) until start of conventional conditioning chemotherapy. Each dot represents the value of one conducted therapy. Shown are box-whiskers blots, *P* - value calculated using t-test.

**TABLES**

**Table 1. Patient characteristics.**

| Patient characteristics | |
|---|---|
| Sex - no. (%) | |
| male | 12 (55) |
| female | 10 (45) |
| Age - yr | |
| median | 54 |
| range | 31 to 68 |
| Diagnosis - no. (%) | |
| AML | 4 (18) |
| MM | 10 (45) |
| DLBCL | 6 (27) |
| MCL | 1 (5) |
| T-PLL | 1 (5) |
| Previous treatment lines - median (range) | 4 (2-9) |
| Patients with previous transplantation - no. (%) | 18 (82) |
| autologous | 12 (55) |
| allogenic | 6 (27) |

no.: number; yr: year; AML: acute myeloid leukemia; MM: multiple myeloma; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; T-PLL: T-cell prolymphocytic leukemia.

**Table 2. Overview of radionuclides, peptides and antibodies**

| Overview of radionuclides, peptides and antibodies | |
|---|---|
| Radionuclide used, no. (%) | |
| $^{177}$Lu-CPCR4 | 6 (24) |
| $^{90}$Y-CPCR4 | 11 (44) |
| $^{90}$Y-CPCR4 + $^{188}$Re-CD66 | 6 (24) |
| $^{90}$Y-CPCR4 + $^{90}$Y-Zevalin | 1 (4) |
| $^{90}$Y-CPCR4 + $^{153}$Samarium-EDTMP | 1 (4) |

**Table 3. Overview of adverse events.**

| Overview of adverse events | |
|---|---|
| Events | no. (%) |
| Any adverse event | 340 |
| Any adverse event of grade ≥ 3 | 86 |
| Adverse event resulting in treatment discontinuation | 1 (4) |

**Table 4. Hematologic toxicities.**

| Hematologic toxicities | |
|---|---|
| Adverse events | no. (%) |
| Anemia | |
| any grade | 25 (100) |
| grade ≥ 3 | 17 (68) |
| Thrombopenia | |
| any grade | 25 (100) |
| grade ≥ 3 | 21 (84) |
| Neutropenia | |
| any grade | 24 (96) |
| grade ≥ 3 | 20 (80) |
| Coagulopathy | |
| any grade | 7 (28) |
| grade ≥ 3 | 0 (0) |

**Table 5. Transplant characteristics.**

| Transplant characteristics | |
|---|---|
| Transplantation type, no. (%) | |
| autologous | 10 (40) |
| allogenic | 14 (56) |
| Time to engraftment, leukocytes, days, mean (range) | |
| autologous | 11.4 (9-14) |
| allogenic | 12.2 (10-20) |
| Time to engraftment, platelets, days, mean (range) | |
| autologous | 14 (9-18) |
| allogenic | 13.25 (10-16) |

Supplemental Material

# Side effects of CXC-chemokine receptor 4 – directed Endoradiotherapy with Pentixather prior to Hematopoietic Stem Cell Transplantation

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**Supplemental - Patients and Methods**

**Rational for repeated Pentixather treatment in two patients**

One patient with very advanced MM received three cycles of CXCR-directed endoradiotherapy of which two were combined with autologous HSCT and one with allogeneic HSCT. The repeated treatment in this patient was conducted due to an initial response to CXCR4-directed endoradiotherapy and the lack of further standard treatment options. In another patient with MM two cycles of CXCR4-directed endoradiotherapy were performed: one cycle prior autologous and one cycle prior allogeneic HSCT. Treatment response to conditioning therapy combined with Pentixather and autologous HSCT was obtained and therefore CXCR4-directed endoradiotherapy was later incorporated into the conditioning regimen prior to allogeneic HSCT.

**Pre-therapeutic Dosimetry**

One or 2 days after the administration of the tracer activity, which was infused without any nephroprotective medication, activity concentrations were measured by quantitative Single Photon Emission Computed Tomography (SPECT)/CT in kidneys, liver, spleen, BM, and, if possible, malignant tissues. Serial planar whole body images were acquired over 3-5 days to deduce the activity kinetics approximated by bi-exponential decay functions in the listed tissues. The decay functions were normalized to the activity concentrations measured by SPECT/CT and integrated to determine the absorbed doses per activity administered. The maximum absorbed doses were deduced for kidneys, BM, and malignant tissues from the highest activity concentrations measured in contiguous volumes of 1 ml. For liver and spleen, mean absorbed doses were measured in large representative volumes within the organs.

All scintigraphic images were acquired with a 20% energy window at 208 keV using dual-head gamma cameras (Siemens Symbia E or Symbia T2) equipped with medium-energy collimators. Whole body images were acquired with 10 cm/min and matrix 256 x 1024. SPECT was measured with matrix 128 x 128, voxel size 4.8 mm (0.11 $cm^3$), and 2 x 60 frames at 30 s per projection with 3° angular step. SPECT data were reconstructed iteratively by 3D-OSEM (6 subsets, 6 iterations) with corrections for scatter and attenuation after a low-dose CT transmission scan.

**Statistical analysis**

All statistical tests were performed using GraphPad Prism (GraphPad Software). P-values < 0.05 were considered statistically significant. Quantitative values were expressed as mean ± standard deviation (SD). Student's t-test was used to compare quantitative data between cohorts.

Due to the retrospective nature of the analysis, the sample size was chosen based on the number of consecutive patients treated with the respective endoradiotherapy in the specified time frame.

**Supplemental Tables**

**Supplemental Table 1.** Dosimetry in $^{177}$Lu-Pentixather treated patients.

**Supplemental Table 2.** Characteristics of the different administered radio-pharmaceuticals.

**Supplemental Table 3.** Higher grade toxicites respective of the administered radiopharmaceuticals

**Supplemental Table 4.** Renal and hepatobiliary toxicities.

**Supplemental Table 5.** Infectious side effects.

**Supplemental Table 6.** Electrolyte disorders.

**Supplemental Table 7.** Gastrointestinal toxicities.

**Supplemental Table 8.** Cardiovascular toxicities.

**Supplemental Table 9.** Toxicities of the nervous system.

**Supplemental Table 10.** Adverse events concerning general disorders.

# Supplemental Table 1

Dosimetry in $^{177}$Lu-Pentixather treated patients

| patient GBq[1] | | kidneys maxV[6] | kidneys mean[7] | liver mean[7] | spleen mean[7] | lesion[8] maxV[6] |
|---|---|---|---|---|---|---|
| #1 | | | | | | |
| 0.24 | Gy/GBq[2] | 1.39 | 1.02 | 0.38 | 0.49 | 3.3 |
| 15.2 | Gy/GBq[3] | 0.69 | 0.57 | 0.37 | 0.47 | 3.5 |
| | Ratio | 50% | 55% | 97% | 96% | 106% |
| | Gy[4] | 10.5 | 8.7 | 5.6 | 7.1 | 53 |
| #2 | | | | | | |
| 0.2 | Gy/GBq[2] | 1.08 | 0.93 | 0.79 | 1.74 | 9.5 |
| 23.5 | Gy/GBq[3] | 0.53 | 0.5 | 0.56 | 1.4 | 3 |
| | Ratio | 49% | 54% | 71% | 80% | 32% |
| | Gy[4] | 12.5 | 11.8 | 13.2 | 32.9 | 70 |
| #3 | | | | | | |
| 0.2 | Gy/GBq[2] | 2.53 | 2.28 | 0.95 | 1 | 4.6 |
| 7.8 | Gy/GBq[3] | 1.53 | 1.57 | 0.75 | 0.81 | 4.8 |
| | Ratio | 60% | 69% | 79% | 81% | 104% |
| | Gy[4] | 11.9 | 12.2 | 5.9 | 6.3 | 37 |
| #4 | | | | | | |
| 0.21 | Gy/GBq[2] | 2.25 | 1.5 | 0.85 | 0.8 | |
| 9.9 | Gy/GBq[3] | 1.62 | 1.1 | 0.63 | 0.73 | |
| | Ratio | 72% | 73% | 74% | 91% | |
| | Gy[4] | 16 | 10.9 | 6.2 | 7.2 | |
| #5 | | | | | | |
| 0.21 | Gy/GBq[2] | 1.36 | 1 | 0.39 | 1.03 | 5.1 |
| 14.6 | Gy/GBq[3] | 0.96 | 0.78 | 0.43 | 0.83 | 4.5 |
| | Ratio | 71% | 78% | 110% | 81% | 88% |
| | Gy[4] | 14 | 11.4 | 6.3 | 12.1 | 66 |
| #6 | | | | | | |
| 0.2 | Gy/GBq[2] | 2.21 | 1.36 | 0.54 | 0.69 | 0.7 |
| 7.6 | Gy/GBq[3] | 1.76 | 1.03 | 0.45 | 0.68 | 0.57 |
| | Ratio | 80% | 76% | 83% | 99% | 81% |
| | Gy[4] | 13.4 | 7.8 | 3.4 | 5.2 | 4.3 |
| mean Ratio[5] (%) | | 64 ± 13 | 68 ± 10 | 86 ± 15 | 88 ± 8 % | 82 ± 30 |

[1)] Patient number and $^{177}$Lu-Pentixather activities for diagnostics and treatment
[2)] Specific absorbed dose in pre-therapeutic dosimetry
[3)] Specific absorbed dose from therapy
[4)] Therapeutic absorbed dose
[5)] Mean ratio of specific absorbed doses in diagnostics and treatment
[6)] Absorbed dose in the contiguous 1 ml volume with the highest activity concentration
[7)] Absorbed dose in entire organ or large representative volume
[8)] Most dominant malignant lesion

# Supplemental Table 2

Characteristics of the different administered radiopharmaceuticals

| radionuclide 1 | radionuclide 2 | application interval | activity radionuclide 1 | activity radionuclide 2 |
|---|---|---|---|---|
| $^{90}$Y-CPCR4 | $^{153}$Samarium-EDTMP | 5 days | 4.7 GBq | 15.9 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 5 days | 2.7 GBq | 7.7 GBq |
| $^{90}$Y-CPCR4 | $^{90}$Y-Zevalin | 1 day | 5.8 GBq | 0.9 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 6 days | 4.5 GBq | 5.2 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 2 days | 5.8 GBq | 5.6 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 5 days | 5.6 GBq | 9.9 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 3 days | 2.4 GBq | 8.6 GBq |
| $^{90}$Y-CPCR4 | $^{188}$Re-CD66 | 5 days | 7.4 GBq | 12.7 GBq |

# Supplemental Table 3

Higher grade toxicites respective of the administered radiopharmaceuticals

| | $^{177}$Lu-CPCR4 | $^{90}$Y-CPCR4 | $^{90}$Y-CPCR4 + $^{188}$Re-CD66 | $^{90}$Y-CPCR4 + $^{153}$Samarium-EDTMP | $^{90}$Y-CPCR4 + $^{90}$Y-Zevalin |
|---|---|---|---|---|---|
| | 6 patients | 11 patients | 6 patients | 1 patient | 1 patient |
| Events, no. (%) | | | | | |
| Anemia | | | | | |
| Grade ≥ 3 | 3 (50) | 8 (80) | 5 (83) | 1 (100) | 0 (0) |
| Thrombopenia | | | | | |
| Grade ≥ 3 | 6 (100) | 7 (64) | 6 (100) | 1 (100) | 1 (100) |
| Neutropenie | | | | | |
| Grade ≥ 3 | 5 (83) | 8 (80) | 5 (83) | 1 (100) | 1 (100) |
| Acute kidney failure | | | | | |
| Grade ≥ 3 | 0 (0) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Proteinuria | | | | | |
| Grade ≥ 3 | 0 (0) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Hypocalcemia | | | | | |
| Grade ≥ 3 | 2 (33) | 2 (18) | 0 (0) | 0 (0) | 0 (0) |
| oral Mucositis | | | | | |
| Grade ≥ 3 | 1 (17) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Arrythmia | | | | | |
| Grade ≥ 3 | 1 (17) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Hypertension | | | | | |
| Grade ≥ 3 | 1 (17) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Hypotension | | | | | |
| Grade ≥ 3 | 0 (0) | 0 (0) | 1 (17) | 0 (0) | 0 (0) |
| Peripheral edema | | | | | |
| Grade ≥ 3 | 0 (0) | 0 (0) | 2 (33) | 0 (0) | 0 (0) |
| Sensory | | | | | |
| Grade ≥ 3 | 0 (0) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Decrease of appetite | | | | | |
| Grade ≥ 3 | 1 (17) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Bleeding | | | | | |
| Grade ≥ 3 | 0 (0) | 1 (9) | 0 (0) | 0 (0) | 0 (0) |
| Infections | | | | | |
| Grade ≥ 3 | 0 (0) | 7 (63) | 2 (33) | 0 (0) | 0 (0) |
| Sweats | | | | | |
| Grade ≥ 3 | 0 (0) | 0 (0) | 1 (17) | 0 (0) | 0 (0) |

## Supplemental Table 4

| Renal and hepatobiliary toxicities | |
|---|---|
| Events | no. (%) |
| Acute kidney failure | |
| any grade | 2 (8) |
| grade ≥ 3 | 1 (4) |
| Proteinuria | |
| any grade | 8 (32) |
| grade ≥ 3 | 1 (4) |
| Hematuria | |
| any grade | 7 (27) |
| grade ≥ 3 | 0 (0) |
| Hyperbilirubinemia | |
| any grade | 6 (24) |
| grade ≥ 3 | 0 (0) |
| Elevation of liver enzymes [ASAT, ALAT, AP] | |
| any grade | 15 (60) |
| grade ≥ 3 | 0 (0) |

# Supplemental Table 5

| Infectious side effects | |
|---|---|
| Adverse events | no. (%) |
| Fever | |
| any grade | 13 (52) |
| grade ≥ 3 | 0 (0) |
| Infections | |
| any grade | 14 (56) |
| grade ≥ 3 | 9 (36) |
| Chills | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Sweats | |
| any grade | 3 (12) |
| grade ≥ 3 | 1 (4) |
| Myalgia / Arthralgia | |
| any grade | 0 (0) |
| grade ≥ 3 | 0 (0) |

# Supplemental Table 6

| Electrolyte disorders | |
|---|---|
| Events | no. (%) |
| Hypoglycemia | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Hyperglycemia | |
| any grade | 22 (88) |
| grade ≥ 3 | 0 (0) |
| Hypocalcemia | |
| any grade | 19 (76) |
| grade ≥ 3 | 4 (16) |
| Hypercalcemia | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Hypokalemia | |
| any grade | 13 (52) |
| grade ≥ 3 | 0 (0) |
| Hyperkalemia | |
| any grade | 7 (28) |
| grade ≥ 3 | 0 (0) |
| Hypomagnesemia | |
| any grade | 10 (40) |
| grade ≥ 3 | 0 (0) |
| Hyponatremia | |
| any grade | 12 (48) |
| grade ≥ 3 | 0 (0) |

# Supplemental Table 7

| Gastrointestinal toxicities | |
|---|---|
| Events | no. (%) |
| Nausea | |
| any grade | 4 (16) |
| grade ≥ 3 | 0 (0) |
| Vomiting | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Diarrhea | |
| any grade | 4 (16) |
| grade ≥ 3 | 0 (0) |
| Constipation | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Oral mucositis | |
| any grade | 10 (40) |
| grade ≥ 3 | 1 (4) |
| Xerostomia | |
| any grade | 2 (8) |
| grade ≥ 3 | 0 (0) |

# Supplemental Table 8

| Cardiovascular toxicities | |
|---|---|
| Adverse events | no. (%) |
| Arrythmia | |
| any grade | 3 (12) |
| grade ≥ 3 | 1 (4) |
| Pericardial effusion | |
| any grade | 5 (20) |
| grade ≥ 3 | 0 (0) |
| Hypertension | |
| any grade | 17 (68) |
| grade ≥ 3 | 2 (8) |
| Hypotension | |
| any grade | 8 (32) |
| grade ≥ 3 | 1 (4) |
| Thrombosis | |
| any grade | 2 (8) |
| grade ≥ 3 | 0 (0) |
| Peripheral edema | |
| any grade | 5 (20) |
| grade ≥ 3 | 2 (8) |

# Supplemental Table 8

| Infectious side effects | |
|---|---|
| Adverse events | no. (%) |
| Fever | |
| any grade | 13 (52) |
| grade ≥ 3 | 0 (0) |
| Infections | |
| any grade | 14 (56) |
| grade ≥ 3 | 9 (36) |
| Chills | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Sweats | |
| any grade | 3 (12) |
| grade ≥ 3 | 1 (4) |
| Myalgia / Arthralgia | |
| any grade | 0 (0) |
| grade ≥ 3 | 0 (0) |

## Supplemental Table 9

| Toxicities of the nervous system | |
|---|---|
| Adverse events | no. (%) |
| Sensory | |
| any grade | 2 (8) |
| grade ≥ 3 | 1 (4) |
| Motory | |
| any grade | 6 (24) |
| grade ≥ 3 | 0 (0) |
| Consciousness | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Headache | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Vertigo | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Insomnia | |
| any grade | 7 (28) |
| grade ≥ 3 | 0 (0) |

## Supplemental Table 10

| General disorders | |
|---|---|
| Adverse events | no. (%) |
| Allergic reaction | |
| any grade | 1 (4) |
| grade ≥ 3 | 0 (0) |
| Decrease of appetite | |
| any grade | 3 (12) |
| grade ≥ 3 | 2 (8) |
| Weight loss | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Weight gain | |
| any grade | 3 (12) |
| grade ≥ 3 | 0 (0) |
| Bleeding | |
| any grade | 7 (28) |
| grade ≥ 3 | 1 (4) |