

Complete hematologic response after belinostat treatment and allogeneic stem cell transplantation for multiple relapsed/refractory angioimmunoblastic T-cell lymphoma: a case report

Vincent Camus¹, Pascaline Etancelin¹, Fanny Drieux¹, Elena-Liana Veresezan², Jean-Michel PICQUENOT², Dominique Penther¹, Mathieu Viennot¹, Philippe Ruminy¹, Nathalie Contentin¹, Emilie Lemasle¹, stephane lepretre³, Sydney Dubois¹, Juliette Penichoux¹, Aspasia Stamatoullas¹, Alexandra Zduniak¹, Helene Lanic¹, and Fabrice Jardin¹

¹Centre Henri Becquerel

²(4) Department of Pathology, Centre Henri Becquerel, Rouen,

³INSERM U1245

April 28, 2023

Title page

Journal: Clinical Case Reports

Article type: Case report

Title: Complete hematologic response after belinostat treatment and allogeneic stem cell transplantation for multiple relapsed/refractory angioimmunoblastic T-cell lymphoma: a case report

Authors: Vincent Camus¹, Pascaline Etancelin², Fanny Drieux³, Elena-Liana Veresezan³, Jean-Michel Picquenot³, Dominique Penther², Mathieu Viennot⁴, Philippe Ruminy⁴, Nathalie Contentin¹, Emilie Lemasle¹, Stéphane Leprêtre¹, Sydney Dubois¹, Juliette Penichoux¹, Aspasia Stamatoullas¹, Alexandra Zduniak¹, Hélène Lanic¹, Fabrice Jardin¹.

Affiliations:

¹ Department of Hematology, Centre Henri Becquerel, Rouen, France.

² Department of Genetic Oncology, Centre Henri Becquerel, Rouen, France.

³ Department of Pathology, Centre Henri Becquerel, Rouen, France.

⁴ INSERM U1245, Centre Henri Becquerel, Rouen, France.

Corresponding author:

Vincent Camus (VC), Department of Hematology, Centre Henri Becquerel, rue d'Amiens, CS 11516, 76038 Rouen Cedex 1, France; vincent.camus@chb.unicancer.fr

Word count (core body): 3,042

Figure count: 5

Reference count: 25

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding statement

The publication of this work was sponsored by IDEOGEN AG (Switzerland).

Conflict of interest statement

Vincent Camus received honoraria from IDEOGEN AG (Switzerland).

The other authors declare no conflict of interest regarding this manuscript.

Ethics approval statement

Not applicable.

Patient consent statement

This case report was published with written consent of the patient.

Abstract

Peripheral T-cell lymphomas have an aggressive disease course associated with poor outcomes. We report a young patient with highly pretreated relapsed/refractory nodal follicular helper T-cell lymphoma (angioimmunoblastic-type [nTFHL-AI]), who successfully received an allogeneic stem cell transplantation following belinostat therapy. The complete hematologic response achieved has lasted more than two years.

Keywords: PTCL, nTFHL-AI, belinostat, HDAC inhibitor, allogeneic stem cell transplantation, complete response

Key clinical message:

This case report highlights the potential of belinostat for the treatment of relapsed/refractory peripheral T-cell lymphomas, for which effective therapies are still scarce.

Introduction

Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of highly aggressive non-Hodgkin lymphomas (NHL). With a 5-year survival rate of approximately 30%, they are associated with poor treatment outcome¹. The most common subtypes of PTCL include nodal follicular helper T-cell (nTFH) lymphoma whose prototype is nTFHL angioimmunoblastic-type (nTFHL-AI), PTCL not otherwise specified (PTCL-NOS), and anaplastic large cell lymphoma (ALCL)^{2, 3}. For decades, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard first-line therapy of PTCL. Although efforts have been made to improve treatment outcomes by replacing CHOP with another chemotherapy regimen or adding new therapeutic agents, limited progress has been made⁴. In recent years, new innovative agents specifically designed for the treatment of relapsed/refractory (R/R) PTCL have received accelerated approval in the United States; they include pralatrexate (a folate antagonist), brentuximab vedotin (an antibody-drug conjugate targeting CD30 protein), and the histone deacetylase inhibitors (HDACis) romidepsin and belinostat⁵⁻⁸. However, most patients with PTCL still experience relapse, and durable, well-tolerated disease control is achieved in only a minority of them⁹. Promising phase II clinical trials with the HDAC inhibitor belinostat as monotherapy showed durable response rates with a manageable safety profile in heavily pretreated PTCL patients^{8, 10}.

In this report, we describe the case of a young patient with multiple pretreated R/R nTFHL-AI, who successfully received an allogeneic stem cell transplantation after belinostat therapy and achieved a durable complete hematologic response.

Case presentation

Medical history

In May 2018, a 33-year-old patient consulted the Department of Infectious Diseases at Jacques Monod hospital (Le Havre, France) with complaints of persistent fever ranging from 38-39 °C since May 2018, night sweats within the last two months, pruritus since April 2018, and recent weight loss of 7 kg (actual weight of 80 kg). Despite undergoing antibiotic therapy, he did not experience any improvement. At the time of consultation, his general health status was classified as performance status (PS) grade 1. The patient's medical history revealed that he had a Crohn's disease, which had been well controlled with adalimumab for approximately 30 months. Although an initial suspicion of an Epstein-Barr virus (EBV) infection was raised, serology showed a negative virus load. The patient did not present any allergies or any intoxication with alcohol or tobacco. In his family history, his father had a sarcoidosis, and an aunt on the maternal family side had lymphoma (unknown subtype).

Diagnostic procedures

In June 2018, a positron emission tomography combined with a computed tomography (PET-CT) scan revealed an intense hypermetabolism of the supra- and subdiaphragmatic lymph nodes, splenomegaly, at least two pulmonary nodules, and an involvement of the entire skeleton to a lesser extent. Consequently, the patient was referred to the Hematology Department of Centre Henri Becquerel (a hospital in Rouen, France) for further evaluation of the suspected lymphatic disease. In July 2018, after an initial biopsy in the left groin and molecular-pathological analyses of the sample, the patient was diagnosed with an nTFHL-AI (**Fig. 1**), with the Ann-Arbor stage being classified as IV. A clonality test identified a low-intensity T-cell receptor gamma (TCR- γ) rearrangement. According to a RACE (rapid amplification of cDNA ends) analysis, a dominance of a TCR-beta clone (43% of detected TCRs) were detected (**Fig. 2A**). Next-Generation Sequencing (NGS) revealed a mutation in *RHOA* (c.50G > T, p.Gly17Val, Tier 2) as well as a detrimental *TET2* mutation (c.4138C>A, p.His1380Asn, Tier 2) with allele frequencies of 13% and 17%, respectively. No informative karyotyping could be performed. Gene expression profiling (GEP) assay confirmed nTFHL-AI signature with *RHOA* G17V hotspot mutation¹¹ (**Fig. 3**). Moreover, a reassessment PET-CT in August 2018 (**Fig. 4**) revealed an increase in supra- and subdiaphragmatic lymphadenopathies and multiple jugulocarotid-, sub-maxillary-, and spinal adenomegalies (max. 11 mm). In addition, multiple mediastinal (17 mm) and axillar pulmonal lesions (16 mm) on the right side, as well as a pathological hypermetabolism in liver and bone were detected. A bone marrow biopsy (BMB) showed a lymphoid infiltration of the bone marrow, but no malignant bone lesions were observed. A blood analysis at that time showed a moderate microcytic anemia (11 g/dl) and light alteration of the renal function (creatinine, 110 μ mol/L), as well as elevated lactate dehydrogenase (LDH) (530 U/L) and C-reactive protein (CRP) (32 mg/L) levels. The patient was in good general condition (PS1).

Treatments and outcome

At the end of August 2018, an improvement of the patient's B-symptoms (weight loss, fever, night sweats, and pruritus) was observed following a corticoid therapy that had been started two weeks earlier. Six cycles of first-line chemotherapy were administered between September and December 2018 using the CHOEP protocol (cyclophosphamide [750 mg/m², Day 1], doxorubicin [50 mg/m², Day 1], etoposide [100 mg/m², Day 1 to Day 3], vincristine [1.4 mg/m², Day 1], and prednisone [40 mg/m², Day 1 to Day 5]), as well as four prophylactic methotrexate (15 mg) intrathecal injections. After three cycles of CHOEP in 3-week cycles, a partial response (PR) occurred with the disappearance of liver and bone hypermetabolism, with a Deauville score (DS) of 5 (DS5). After three additional cycles of CHOEP, a progressive disease (PD) was observed in form of a hypermetabolic state of the spleen hilum with a DS5. However, lymphadenopathies above and below the diaphragm persisted, in addition to the onset of a new hypermetabolism in the splenic hilum lymph nodes. A second biopsy of the right axilla was performed in January 2019 which confirmed the persistence of an nTFHL-AI. A new RACE analysis showed the persistence of the dominant TCR-beta clone (30-35%) and detected two very low-abundant TCR-beta clones (0.5%) and one TCR-delta clone (6%) (**Fig. 2B**). The following karyotype was established on the lymph node biopsy 52,XY,+5,+10,+15,+17+18+21[4]/46,XY[18], trisomy 5 and trisomy 21 being consistent with an nTFHL-AI diagnosis¹².

From mid-February to end of April 2019, the patient received three cycles of gemcitabine (1200 mg/m², Day 1, Day 8, and Day 15) as second-line therapy. At the start of the therapy, the patient was in good general health (PS0), but his condition slightly deteriorated in mid-May 2019 (PS1) with the apparition of a facial edema without vena cava syndrome. A follow-up PET-CT in May 2019 showed progressive disease (PD) with an increase in size (23 x 15 mm cervical, 22 x 21 mm axillar, 20 x 40 mm sub-carinar), number, and intensity of the supra- and subdiaphragmatic lymph node hypermetabolism (DS5).

Subsequently, a third-line chemotherapy with ICE regimen (ifosamide [5 g/m², Day 2], carboplatin [AUC 5 mg/ml.min, Day 2], and etoposide [100 mg/m², Day 1 to Day 3]) was administered from mid-May to late June 2019; this new therapy was well tolerated and resulted in a PR with a DS4 after three cycles, as confirmed by a new PET-CT.

The PR allowed for a BEAM (carmustine, etoposide, cytarabine, and melphalan)-conditioned autologous transplantation to be performed at the end of July 2019. However, this transplantation failed, and, in August 2019, a follow-up PET-CT showed a major PD with a DS5. A biopsy of a right inguinal lymph node revealed the persistence of the nTFHL-AI. The RACE analysis showed the dominance of the two original minor TCR-beta clones (14% each), while the TCR-beta clone that was dominant in 2018 had declined to 5-6%. Additionally, a TCR-delta clone was again detected at 2.4%, and a new TCR-alpha clone also appeared at 4.5% (**Fig. 2C**). Finally, the *RHOA* gene mutation was still detected by NGS.

Because of the presence of the *TET2* mutation¹³, a treatment with azacytidine (75 mg/m², Day 1 to Day 7) – a hypomethylating agent – was then initiated end of September 2019 and administered until mid-January 2020 with the goal of subsequently performing an allogeneic stem cell transplantation (allo-SCT). After the first cycle of azacytidine, the PET-CT performed by the end of October 2019 initially showed a complete metabolic response (CMR) with a DS3. However, further therapy with azacytidine was suboptimal. Bacteremia (*Staphylococcus haemolyticus*) of the implanted central venous access port (CVAP) was diagnosed in December 2019, which completely resolved following the administration of daptomycin (10 mg/kg) for 14 days. However, patients remained transfusion-dependent with severe pancytopenia. Due to a new episode of antibiotic/antifungal therapy-resistant and prolonged febrile aplasia, a BMB was performed in February 2020 and showed a bone marrow infiltration by the nTFHL-AI. PET-CT only revealed an intense and heterogeneous uptake of the bone marrow without any lymph node involvement.

Due to PD proven on BMB, the allo-SCT was postponed, and the decision was made to treat the patient with belinostat through a managed access program. Between the end of February 2020 and September 2020, a total of eight cycles of belinostat (1,000 mg/m², Day 1 to Day 5 of a 21-day cycle) were administered. The treatment with belinostat was well tolerated and the patient's general condition improved significantly over the course of therapy. Follow-up PET-CT analyses showed minimal progression after Cycle 2 (DS5) (**Fig. 5A**) resembling “tumor flare” (pseudo-progression) with complete disappearance of B-symptoms and clinical improvement, PR after Cycle 4 and Cycle 6 (both DS4) (**Fig. 5B, Fig. 5C**) with BMB complete response at the end of July 2020, and minimal progression after Cycle 8 (DS5) (**Fig. 5D**). Another BMB performed at the end of September 2020 confirmed persistent complete response at the bone marrow level. The patient was clinically considered to present a very good partial response, with no nTFHL-AI-related symptoms; therefore, a decision was made to perform a consolidation allo-SCT at the end of October 2020.

We utilized an adapted TEC-RIC sequential conditioning regimen consisting of a sequential chemotherapy with thiotepa (5 mg/kg, Day-14), etoposide (100 mg/m², Day-13 to Day-10), and cyclophosphamide (400 mg/m², Day-13 to Day-10) (TEC) followed by a reduced intensity conditioning (RIC) regimen with fludarabine (150 mg/m², i.v.), busulfan (6.4 mg/kg), and thymoglobulin (5 mg/kg, Day-6 to Day-2). The donor was a 10/10 matched unrelated donor and we used peripheral blood stem cell (PBSC) donation. Both donor and recipient presented with a blood group O+, a negative cytomegalovirus (CMV) serology, as well as a positive serology for the Epstein-Barr virus (EBV) in favor of a prior EBV immunity. As prophylaxis of the graft-versus-host (GvH) disease, the patient received anti-thymocyte globulin (ATG) pre-allo-SCT, as well as cyclosporine 3mg/kg/day and mycophenolate mofetil 1000mg twice per day post-allo-SCT. However, during the transplant, a hepatic veno-occlusive disease with a severity of 6 out of 12 criteria on the hepatic Doppler-

ultrasonography¹⁴ and a high level of total bilirubin of 51 $\mu\text{mol/l}$ (normal value $< 21 \mu\text{mol/l}$ on November 7, 2020) was diagnosed and showed a favorable course under defibrotide (25 mg/kg/day for 1 month). Additionally, the patient experienced a severe and acute GvH disease of the skin (grade 3) and in the digestive tract including a rectorrhagia (grade 4, with a hemorrhagic shock which required a transfer to the intensive care unit). Histological analyses confirmed the cutaneous and digestive (from colonic biopsies through digestive endoscopy and colonoscopy) GvH disease which responded well to corticosteroids (the patient received 2 mg/kg/day of prednisone for two weeks). Progressive discontinuation of corticosteroids led to a recurrence of minimal cutaneous GvH reactions. A post-transplant PET-CT performed at the end of November 2020 (Day+30) demonstrated a partial regression of the hypermetabolic lymph node metabolism on the right side, as well as a complete regression of the other metabolisms (DS4, partial metabolic response). Complete donor chimerism was achieved at Day+30 with donor/host chimerism results of 99.7% of the total blood population/100.0% of the myeloid population/96.0% of the lymphoid population, and 100.0/100.0/99.3%, respectively, at Day+100. Due to an EBV reactivation, the patient had to receive four weekly injections of rituximab (375 mg/m², Day 1, Day 8, Day 15, and Day 21), the last one in mid-December 2020. No EBV recurrence happened after. Despite a minimal persistent mucosal GvH disease, a withdrawal of the corticosteroids (4 months post-allo-SCT on February 26, 2021) and of the immunosuppressors (on June 4, 2021, for the mycophenolate mofetil, and on August 16, 2021, for the cyclosporine) was performed. Although a high risk of relapse post-allo-SCT existed, neither a reinjection of donor lymphocytes post-allo-SCT – because of the prior severe digestive GvH disease –, nor a belinostat maintenance therapy – because maintenance is not a standard of care in T-cell lymphoma –, were considered.

At his last follow-up appointment in October 2022 - two years after the allo-SCT - the complete hematologic response was confirmed. No further GvH reactions occurred, and a non-severe post-transfusional hemochromatosis (ferritin, 3,420 ng/mL) was treated with monthly phlebotomies of 400 mL. The patient stated that he was looking forward for work, exercising regularly on his exercise bike, and seeing a urologist for a libido disorder. His next control visit at the hospital is planned in May 2023.

Discussion

We reported here a very rare case of a heavily refractory nTFHL-AI in a young patient that was successfully treated with belinostat and consolidation allo-SCT. The diagnosis of nTFHL-AI in this patient was unusual due to his young age (33 years), as the median age at diagnosis of nTFHL-AI in the literature is 65 years¹⁵.

Because of the rarity and heterogeneity of PTCL, few randomized clinical trials are available. Thus, strategies for first-line treatment have often been adopted from treatment paradigms for aggressive B-cell lymphomas¹⁶. Anthracycline-based therapeutic regimens such as CHOP or CHOEP are still commonly used as first-line therapy, but their efficacy in PTCL has not been prospectively proven, and generally does not lead to durable remissions¹⁷. The role of autologous stem cell transplantation as a first-line treatment in patients achieving complete or partial response is still highly debated, all reports suffering from both positive and negative biases. Patients undergoing an allo-SCT are usually fitter, younger, and have responded well to induction regimens, but they may also present with more aggressive disease features than patients who do not undergo an allo-SCT. On the other hand, an allo-SCT usually offers the chance of long-term remission for eligible patients in the R/R setting. Promising results have been achieved with a 2- and 5-year PFS of 45% and 53%, respectively, in nodal PTCL, and up to 81% in nTFHL-AI; however, only few patients are eligible for this therapy⁹. The patient described in this case report did not achieve a disease control even after undergoing three different commonly used lines of therapy (CHOEP, gemcitabine, ICE) and an autologous transplantation. Additional therapy with the hypomethylating agent azacytidine, which was expected to induce a good response due to the presence of a *TET2* mutation, was also not successful¹³. After several prior treatments, it was the belinostat therapy which induced a sufficient response to allow the patient to get an allo-SCT; this clinical case is, however, a good illustration of a graft-versus-leukemia (GvL) effect of the allo-SCT in nTFHL-AI. Before the allo-SCT, we had concerns about a higher risk for a digestive GvH disease because of the patient's medical history of Crohn's disease; however, since the allo-SCT, the patient did not present any further Crohn's disease onset, although he did not receive any specific therapy (no mesalamine

treatment) since the allo-SCT.

The HDAC inhibitor belinostat was first approved by the U.S. FDA in 2014 for the treatment of R/R PTCL; it inhibits the tumor cell growth by inducing cell cycle arrest and apoptosis. In addition, the inhibition of HDAC causes a histone acetylation, leading to an increased expression of tumor suppressor genes¹⁸. Compared to other HDAC inhibitors that selectively inhibit specific HDAC enzymes (such as the class-I selective HDACi romidepsin), belinostat is a pan-HDAC inhibitor that blocks all zinc-dependent HDAC enzymes with high affinity. It is believed that a broader spectrum of inhibition results in better efficacy¹⁹. The phase II BELIEF clinical study evaluated belinostat as monotherapy in 120 patients with R/R PTCL and demonstrated an overall response rate (ORR) of 26% (complete response, CR: 10.8%) with a median duration of response (DoR) of 13.6 months (95% CI, 4.5-29.4)⁸. An impressive case of an elderly patient with a chemorefractory PTCL showed a particularly long-lasting efficacy of over 39 months after treatment with belinostat²⁰. Among the PTCL patients enrolled in the BELIEF trial, 22 patients had nTFHL-AI; an analysis of this subgroup showed an even higher ORR of 45% (CR: 18%) compared with the overall study population²¹.

nTFHL-AI has been associated with frequent mutations in epigenome-regulating genes, such as *TET2* (80%), *DNMT3A* (20% to 30%), *IDH2* (20% to 30%) and *RHOA* (50% to 70%)²². It is suggested that HDAC inhibitors may help maintain an acetylated and active *TET2* and therefore prevent the abnormal DNA methylation that occurs in cancer²¹. Using a gene set cancer analysis (GSCALite), both *TET1* and *TET2* genes were shown to be sensitive to belinostat^{23, 24}. Mutations in *TET2* and *RHOA* were also present in our patient case, and the use of belinostat may have eventually led to a very good partial response of the disease, allowing an allo-SCT to be performed. A sub-analysis of the BELIEF study presented data from patients who underwent a hematopoietic SCT (HSCT) after belinostat treatment: a total of twelve patients, including two patients with nTFHL-AI, received either an autologous SCT (4 patients) or an allo-SCT (8 patients). In total, one patient achieved a PR with an overall survival (OS) of 19.9 months, and one patient was not evaluable with an OS of 9.4 months²⁵.

This is, to our knowledge, the first report of an allo-SCT following belinostat therapy in a young patient presenting with a multiple R/R nTFHL-AI that resulted in a durable CR. Our patient has been able to maintain a complete hematologic response for at least two years, up to the writing of this case report.

Conclusion

Multiple R/R PTCLs are difficult to treat, and the chances of a successful outcome are quite low. Currently, there is no clear consensus on the optimal treatment strategy, and physicians must rely on existing clinical trials or case reports. In recent years, research has shown that genomic profiling of tumors is essential for the selection of appropriate, tailored, and targeted therapy. We present here a case of a young father with nTFHL-AI who achieved a durable and stable response with belinostat treatment followed by an allo-SCT after multiple unsuccessful prior treatment regimens. This highlights the efficacy of belinostat in R/R nTFHL-AI setting, particularly in the presence of epigenetic alterations such as *TET2* or *RHO* and makes it a potential promising therapeutic option as preparation for a planned allo-SCT.

Acknowledgements

The authors would like to thank Florence Boulmé, PhD, for writing assistance.

Authorship list

VC wrote the manuscript; MV and PR performed RACE analyses; PE performed NGS and GEP analyses; DP performed karyotype analyses; FD, JMP and ELV performed histopathological analyses. HL, NC, EL, SL, SD, JP, AS, HT and FJ were involved in the care of the patient. All authors read, reviewed, and approved the final manuscript.

References

1. Savage, K. J. 2007. Peripheral T-cell lymphomas. *Blood Rev* 21:201-216.

- 2.** Alaggio, R., Amador, C., Anagnostopoulos, I., et al. 2022. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia* 36:1720-1748.
- 3.** Foss, F. 2011. Evolving Therapy of Peripheral T-cell Lymphoma: 2010 and beyond. *Ther Adv Hematol* 2:161-173.
- 4.** Sibon, D. 2022. Peripheral T-Cell Lymphomas: Therapeutic Approaches. *Cancers (Basel)* 14.
- 5.** O'Connor, O. A., Pro, B., Pinter-Brown, L., et al. 2011. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 29:1182-1189.
- 6.** Pro, B., Advani, R., Brice, P., et al. 2012. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 30:2190-2196.
- 7.** Piekarz, R. L., Frye, R., Prince, H. M., et al. 2011. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 117:5827-5834.
- 8.** O'Connor, O. A., Horwitz, S., Masszi, T., et al. 2015. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. *J Clin Oncol* 33:2492-2499.
- 9.** Moskowitz, A. J. 2019. Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma. *J Oncol Pract* 15:137-143.
- 10.** Foss, F., Advani, R., Duvic, M., et al. 2015. A Phase II trial of Belinostat (PXD101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. *Br J Haematol* 168:811-819.
- 11.** Drieux, F., Ruminy, P., Abdel-Sater, A., et al. 2020. Defining signatures of peripheral T-cell lymphoma with a targeted 20-marker gene expression profiling assay. *Haematologica* 105:1582-1592.
- 12.** Schlegelberger, B., Zhang, Y., Weber-Matthiesen, K., et al. 1994. Detection of aberrant clones in nearly all cases of angioimmunoblastic lymphadenopathy with dysproteinemia-type T-cell lymphoma by combined interphase and metaphase cytogenetics. *Blood* 84:2640-2648.
- 13.** Itzykson, R., Kosmider, O., Cluzeau, T., et al. 2011. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia* 25:1147-1152.
- 14.** Lassau, N., Auperin, A., Leclere, J., et al. 2002. Prognostic value of doppler-ultrasonography in hepatic veno-occlusive disease. *Transplantation* 74:60-66.
- 15.** Federico, M., Rudiger, T., Bellei, M., et al. 2013. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol* 31:240-246.
- 16.** Moskowitz, A. J., Lunning, M. A., Horwitz, S. M. 2014. How I treat the peripheral T-cell lymphomas. *Blood* 123:2636-2644.
- 17.** O'Leary, H. M., Savage, K. J. 2008. Novel therapies in peripheral T-cell lymphomas. *Curr Oncol Rep* 10:404-411.
- 18.** Lee, H. Z., Kwitkowski, V. E., Del Valle, P. L., et al. 2015. FDA Approval: Belinostat for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma. *Clin Cancer Res* 21:2666-2670.
- 19.** Bolden, J. E., Peart, M. J., Johnstone, R. W. 2006. Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov* 5:769-784.
- 20.** Reimer, P., Chawla, S. 2013. Long-term complete remission with belinostat in a patient with chemotherapy refractory peripheral T-cell lymphoma. *J Hematol Oncol* 6:69.
- 21.** Sawas, A., Ma, H., Shustov, A., et al. 2020. Characterizing the belinostat response in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. *Leuk Lymphoma* 61:2003-2007.

- 22.** Lemonnier, F., Gaulard, P., de Leval, L. 2018. New insights in the pathogenesis of T-cell lymphomas. *Curr Opin Oncol* 30:277-284.
- 23.** Liu, C. J., Hu, F. F., Xia, M. X., et al. 2018. GSCALite: a web server for gene set cancer analysis. *Bioinformatics* 34:3771-3772.
- 24.** Huang, Y., Wei, J., Huang, X., et al. 2020. Comprehensively analyze the expression and prognostic role for ten-eleven translocations (TETs) in acute myeloid leukemia. *Transl Cancer Res* 9:7259-7283.
- 25.** Shustov, A., Al-Ali, H., Wulf, G., et al. 2014. Subsequent Hematopoietic Stem Cell Transplantation in Belinostat-Treated Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma (R/R PTCL). *Blood* 124.

Figures

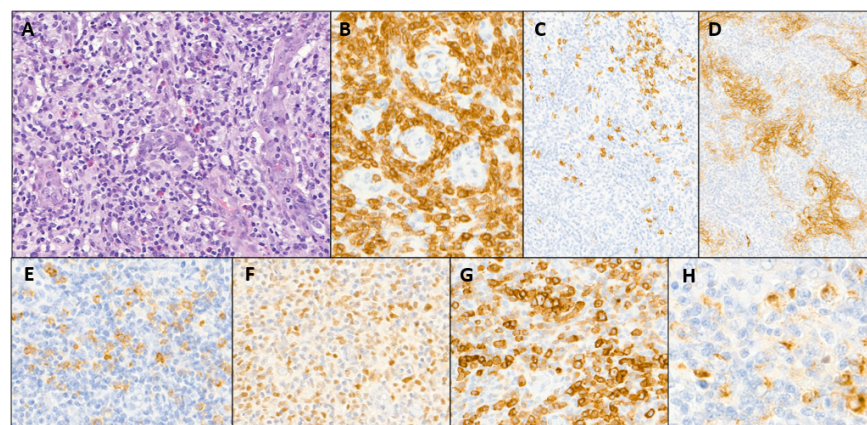
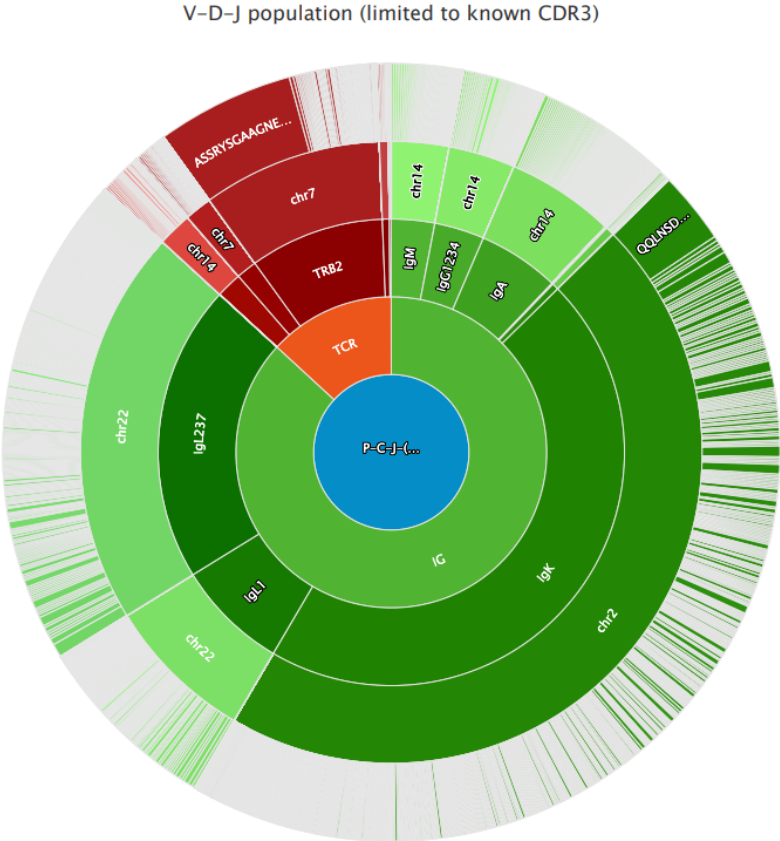


Figure 1 . Biopsy at diagnosis. **A)** The lymph node architecture is completely effaced by a polymorphous infiltrate, composed of small reactive lymphocytes, histiocytes, eosinophils, plasma cells and small to medium size atypical lymphocytes adjacent to high endothelial venules (HE x 400) **B)** Atypical T-cell lymphocytes expressed CD3 **C)** CD20 immunostaining showed scarce B-cell lymphocytes **D)** CD21 highlighted an extensive follicular dendritic cells meshwork **E-H)** Expression of TFH markers by the atypical T-cells (E:CD10, F: BCL6, G: PD1, H: CXCL13)

Figure 2. A) Rapid amplification of cDNA ends (RACE) analysis at diagnosis (July 2018) showing a dominance of a TCR-beta clone (43% of detected TCRs). **B)** RACE analysis at first relapse (January 2019) showing the persistence of the dominant TCR-beta clone (30-35%) and the detection of two very low-abundant TCR-beta clones (0.5%) and one TCR-delta clone (6%). **C)** RACE analysis at 2nd relapse showing the dominance of the two original minor TCR-beta clones (14% each), while the TCR-beta clone that was dominant in 2018 had declined to 5-6%. Additionally, a TCR-delta clone was again detected at 2.4%, and a new TCR-alpha clone also appeared at 4.5%. This suggest a sub clonal evolution of the disease.

A)

B)



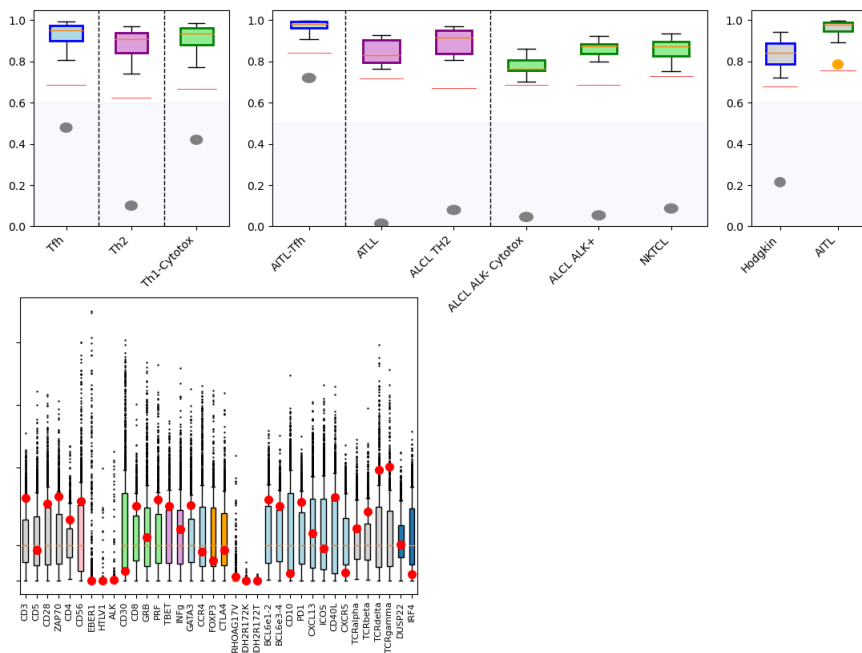


Figure 4. Initial PET-CT performed in August 2018 showing intense hypermetabolism of the supra- and subdiaphragmatic lymph nodes, splenomegaly, at least two pulmonary nodules, and to a lesser extent of the entire skeleton.

PET-CT, positron emission tomography - computed tomography.

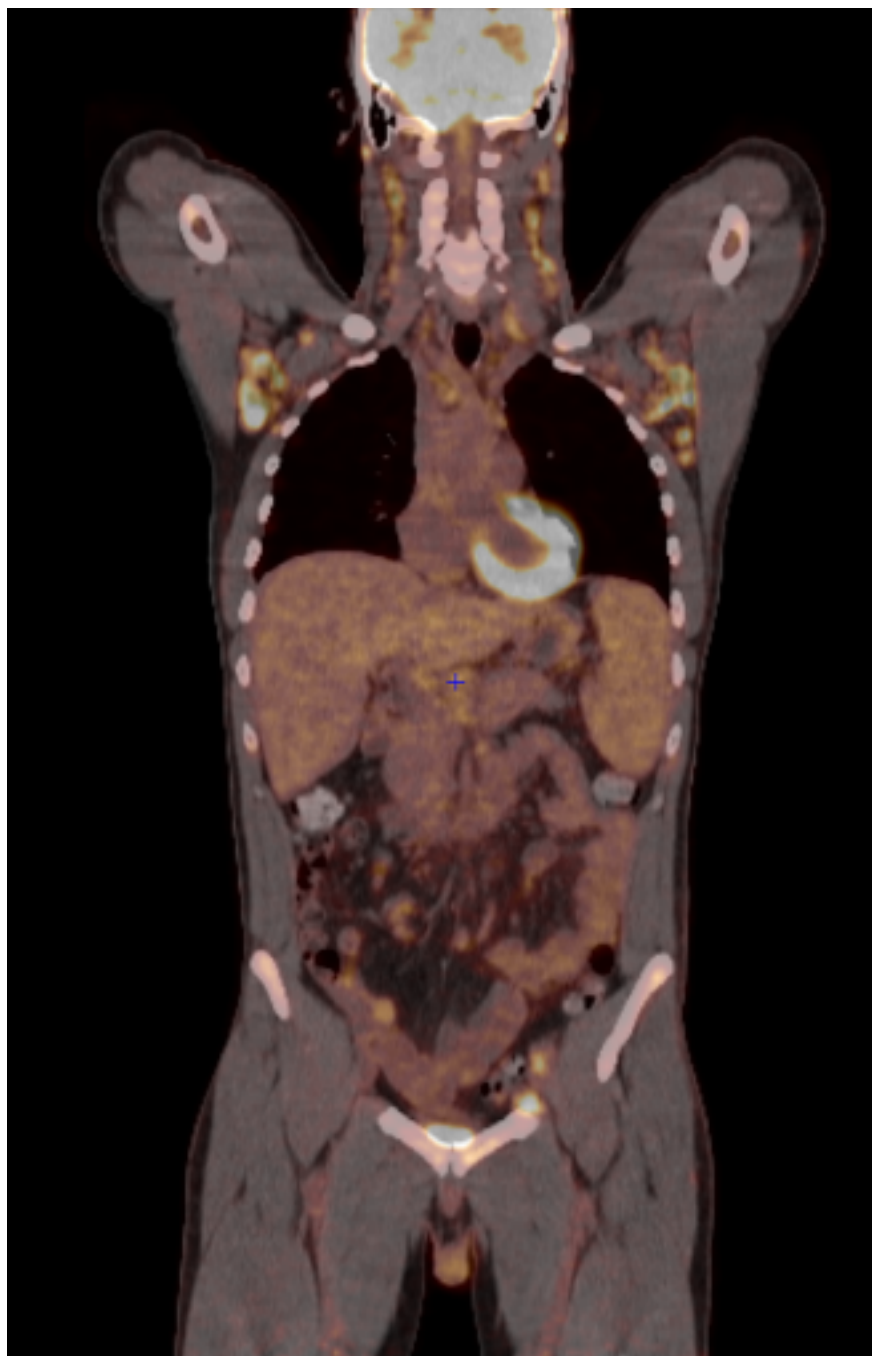
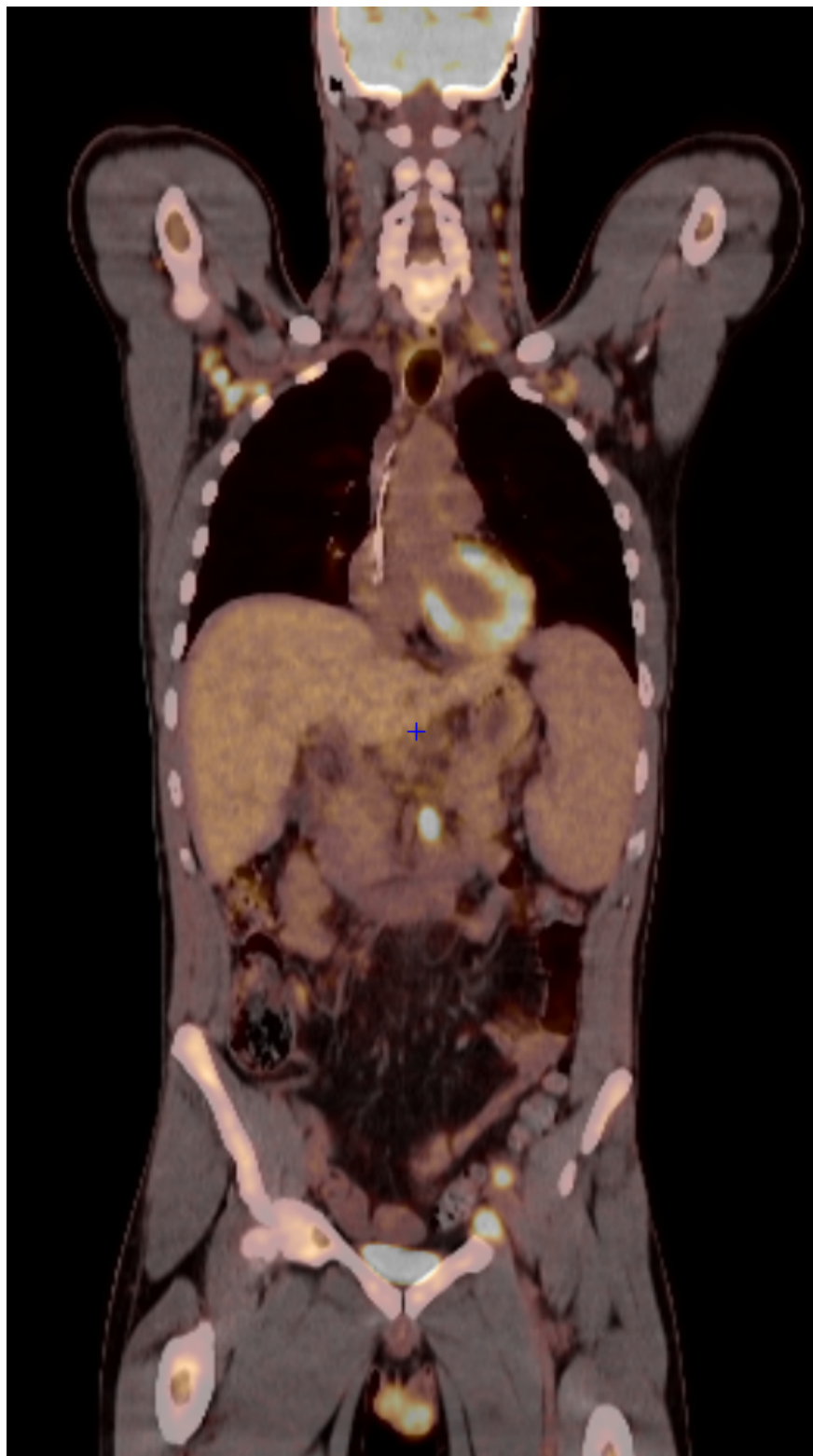


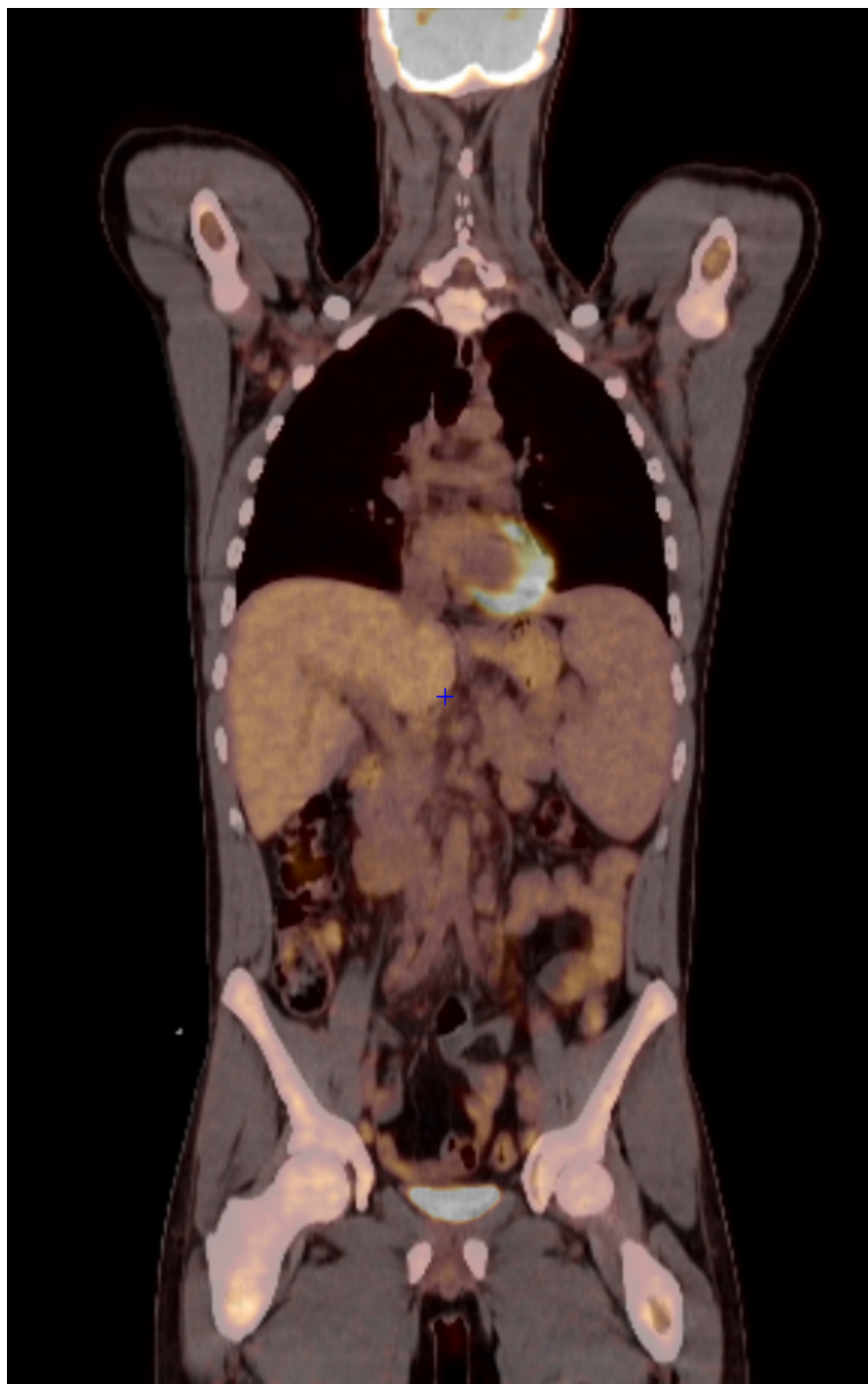
Figure 5. PET-CT performed during belinostat therapy (1,000 mg/m²): **A)** after two cycles of belinostat therapy (DS 5, April 2020); **B)** after four cycles of belinostat therapy (DS 4, June 2020); **C)** after six cycles of belinostat therapy (DS 4, August 2020); **D)** after eight cycles of belinostat therapy (DS 5, September 2020).

PET-CT, positron emission tomography - computed tomography; DS, Deauville score.

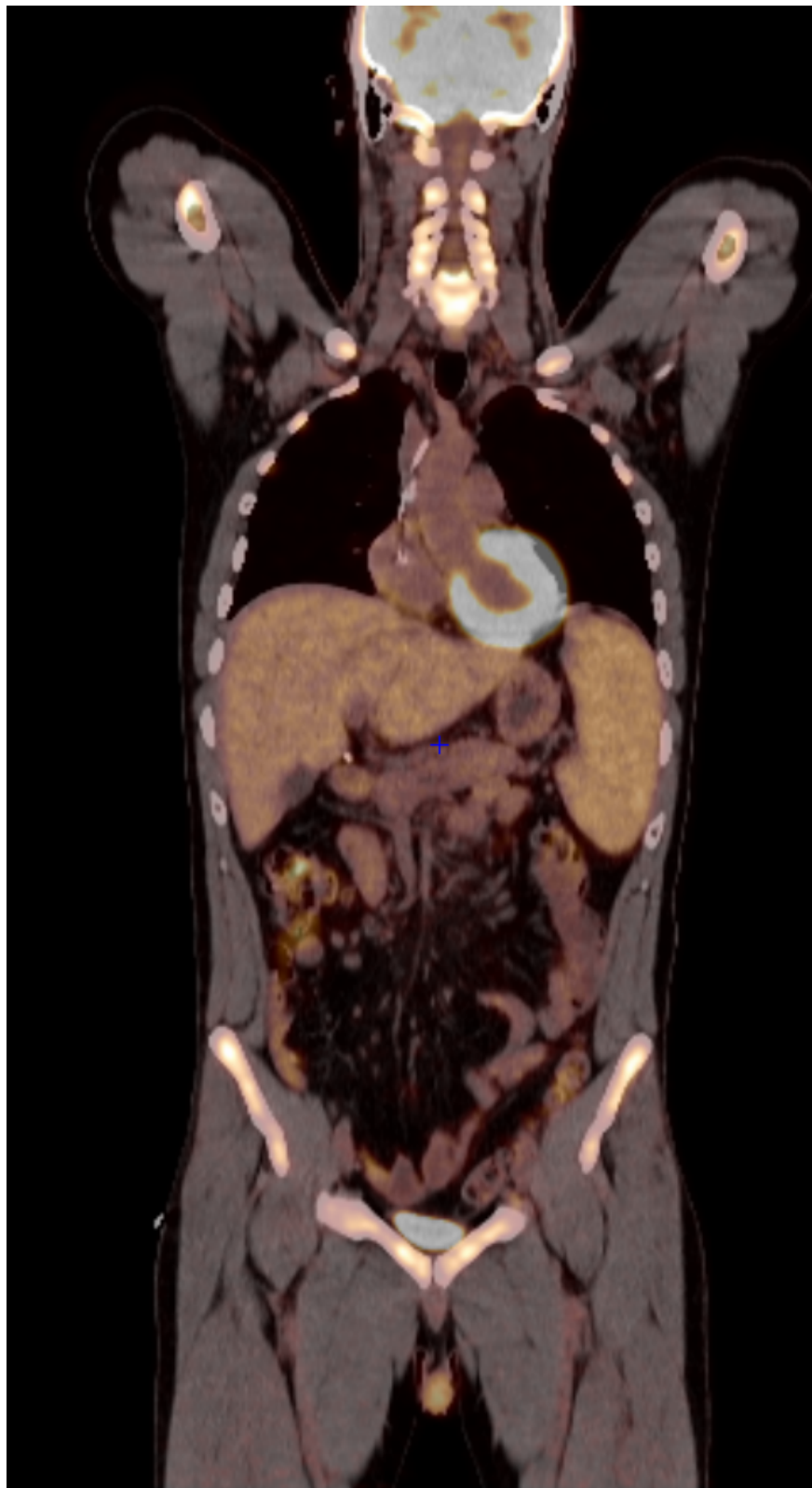
(A) After Cycle 2



(B) After Cycle 4



(C) After Cycle 6



(D) After Cycle 8

