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# Belinostat in relapsed/refractory peripheral T-cell lymphoma: A real-world multicenter experience

Sureyya Yigit Kaya[a,*], Gulsah Akyol[b], Esra Yildizhan[c], Serhat Celik[d], Huseyin Saffet Bekoz[a], Senem Maral[a], Omur Gokmen Sevindik[e], Leylagul Kaynar[a]

[a]Istanbul Medipol University, Faculty of Medicine, Department of Hematology, Istanbul, Türkiye
[b]Erciyes University, Faculty of Medicine, Department of Hematology, Kayseri, Türkiye
[c]Kayseri City Hospital, Clinic of of Hematology, Kayseri, Türkiye
[d]Ankara Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Department of Hematology, Ankara, Türkiye
[e]Demiroglu Bilim University, Faculty of Medicine, Department of Hematology, Istanbul, Türkiye
*Corresponding author: sureyyayigitkaya@hotmail.com (Sureyya Yigit Kaya)

## MAIN POINTS

- Belinostat demonstrated clinical benefit in a subset of heavily pretreated R/R PTCL patients, with two achieving CR.
- Treatment was well tolerated with no dose reductions or discontinuations due to adverse events.
- This multicenter real-world analysis provides valuable evidence supporting the role of belinostat as a salvage option in advanced R/R PTCL.

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## ABSTRACT

**Aim:** Peripheral T-cell lymphoma (PTCL) is a rare and aggressive subtype of non-Hodgkin lymphoma with limited treatment options, particularly in relapsed/refractory (R/R) cases. Belinostat, a pan-histone deacetylase inhibitor, has emerged as a potential therapeutic agent in this setting.

**Materials and Methods:** This retrospective study analyzed nine patients with relapsed/refractory PTCL treated with belinostat across three centers between 2018 and 2025. Clinical data and treatment outcomes were collected, and responses were evaluated using the Lugano criteria. Overall survival and progression-free survival were calculated with the Kaplan–Meier method.

**Results:** Of the nine R/R PTCL patients treated with belinostat, two (22.2%) achieved complete remission (CR), one (11.1%) experienced stable disease, four (44.4%) developed progressive disease and two (22.2%) died from lymphoma progression before the second cycle could be administered. Notably, one patient maintained a prolonged CR through 14 belinostat cycles, while another continued to use belinostat as a bridge to allogeneic stem cell transplantation and as maintenance after allogeneic transplantation. Belinostat was generally well tolerated, and no treatment discontinuations or dose reductions were required due to adverse events.

**Conclusion:** Although these real-world findings suggest that belinostat may provide meaningful clinical benefit in a subset of heavily pretreated R/R PTCL patients, the high rate of early progression emphasizes the need for improved patient selection and prospective validation in larger studies.

**Keywords:** Peripheral T-cell lymphoma, Relapsed/refractory, Histone deacetylase inhibitors, Belinostat

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## INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is a type of non-Hodgkin lymphoma that arises from post-thymic T cells and is marked by significant heterogeneity. Clinically, PTCLs often exhibit an aggressive clinical course and are associated with poor outcomes [1,2]. According to the 5th edition of the classification of World Health Organization of hematolymphoid tumors, PTCL is categorized within mature T- and NK-cell neoplasms and encompasses several subtypes, each displaying distinct and complex clinicopathological features. Common subtypes of PTCL include not otherwise specified (PTCL-NOS), nodal T follicular helper (TFH) cell lymphoma-angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL) [2]. Despite ongoing research, PTCL therapy remains challenging due to the limited number of available treatment options and their modest efficacy. In recent years, histone deacetylase (HDAC) inhibitors have emerged as novel epigenetic therapeutic agents for both newly diagnosed and relapsed/refractory (R/R) PTCL cases. Their complex mechanisms of action

include inducing cell cycle arrest and apoptosis, promoting cellular differentiation, inhibiting angiogenesis, and modulating cytokine signaling [3,4]. By targeting key pathways underlying the molecular complexity of PTCL, HDAC inhibitors offer a comprehensive approach to suppressing tumor growth and progression [5]. Belinostat is a hydroxamic acid–derived pan-HDAC inhibitor that broadly inhibits all zinc-dependent HDAC enzymes, exhibiting high affinity for class I, II, and IV HDACs [6,7]. In recent years, studies have been conducted to evaluate the safety and therapeutic outcomes of HDAC inhibitor monotherapy or its combination with conventional regimens in patients with untreated or R/R PTCL [7–9]. However, real-world data the use of these agents remain limited. In this study we present data from nine R/R PTCL patients who received belinostat treatment at different centers. These real-world data may provide valuable insights into the patient population receiving advanced-line therapies, which remains underrepresented in clinical trials.

## MATERIALS AND METHODS

### *Study design and patient selection*

This retrospective, multicenter study included nine patients with R/R PTCL. Eligible patients had a histologically confirmed diagnosis of PTCL and received belinostat therapy between 2018 and 2025 at one of the participating centers. Patients with incomplete clinical data or missing follow-up information were excluded from the analysis. Demographic data, prior therapies, bone marrow transplantation history, disease progression status and belinostat outcomes were systematically recorded using a standardized data collection form.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from Istanbul Medipol University Ethics Committee (Date: 22-05-2025, Number: 580).

### *Response evaluation*

Radiologic assessments were conducted at each participating center using computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography–computed tomography (PET) scans, as clinically indicated. Treatment response was evaluated according to the Lugano criteria. Patients underwent PET-CT scanning to assess response after two belinostat cycles and the results were classified as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD). Adverse events were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

### *Statistical analysis*

All calculations were performed using descriptive statistics. Continuous variables are presented as medians (range), while categorical variables are expressed as counts (n) and percentages (%). No further comparative analyses were performed due to the limited sample size. Overall survival (OS) was defined as the time from the date of first belinostat administration to the date of death from any cause. Patients who remained alive at the time of data cutoff were censored at their last known date alive. Progression-free survival (PFS) was defined as the time from first belinostat administration to the date of either documented disease progression or death from any cause, whichever occurred first. Patients without PD or death by the data cutoff were censored at the date of their last tumor assessment. In addition, if a patient initiated a subsequent anticancer therapy prior to experiencing PD or death, they were censored at the date of their final tumor evaluation. OS and PFS were estimated using the Kaplan–Meier method. Statistical analysis was performed using Statistical Package of Social Science (SPSS Inc., Chicago, IL), version 22.0 for Windows.

## RESULTS

A total of nine patients with R/R PTCL were included in this study. The median age at the time of belinostat initia-

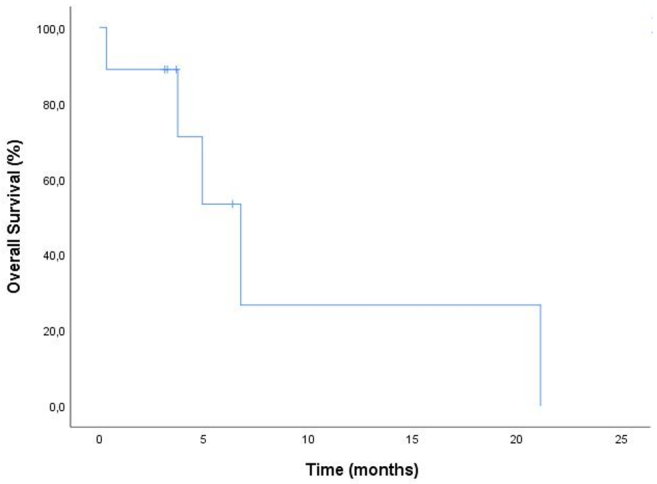


**Figure 1.** The median OS was 6.8 months (95% CI, 3.9 to 9.6).

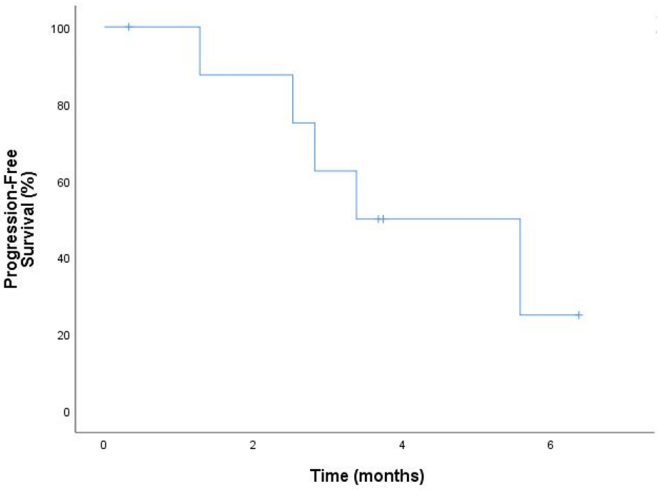


**Figure 2.** The median PFS was 3.4 months (95% CI, 0.8 to 5.6).


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**Table 1.** Patient demographics, previous treatments, and clinical outcomes.

| Patient | Age/ Sex | Stage | PTCL Subgroup | ECOG | Comorbidity | Previous Treatments (response) | Clinical Outcomes and Complications |
|---|---|---|---|---|---|---|---|
| 1 | 65/F | 4 (bone involvement) | PTCL, NOS | 1 | HTN, DM | 3xCHOP (SD)<br>2xICE + RT (PR)<br>2xBelinostat (PD)<br>2xGEMOX (PD)<br>1xPralatrexate<br>(Ongoing treatment) | No AE, Alive |
| 2 | 52/F | 4 (bone and skin involvement) | ALCL, ALK- | 1 | No comorbidity | 6xBV-CHP (CR),<br>BEAM-ASCT (CR)<br>External beam radiation therapy +<br>MTX + 6-MP (CR)<br>2xBV-ICE (CR)<br>3xBelinostat + RT (CR)<br>Allo-SCT (CR) +<br>Maintenance Belinostat | No AE, Alive |
| 3 | 70/M | 3 | PTCL, NOS | 1 | HTN | 4xCHOEP (PD)<br>2xBV-Bendamustine (PD)<br>1xBelinostat (NE) | No AE,<br>Exitus because of lymphoma progression |
| 4 | 78/M | 4 (bone and skin involvement) | ALCL, ALK- | 1 | CHD | 6xCHOP (SD)<br>6xBV-Bendamustine (SD)<br>2xGEMOX (PD)<br>2xBelinostat (PD)<br>RT | No AE,<br>Exitus because of lymphoma progression |
| 5 | 56/F | 3 | PTCL, NOS | 1 | No comorbidity | 5xCHOP (CR)<br>1xICE (PD)<br>1xGEMOX (PD)<br>2xBelinostat (PD)<br>1xPralatrexate (Ongoing treatment)<br>+ IT chemotherapy<br>(ARA-C +<br>Methotrexate + Hydrocortisone) | No AE, Alive |
| 6 | 62/M | 4<br><br>(gastric involvement) | PTCL, NOS | 1 | No comorbidity | 6xCHOP (CR),<br>BEAM-ASCT (CR)<br>6xBV-GDP (CR)<br>Allo-SCT (PD)<br>4xBelinostat (SD)<br>2xRomidepsin (PD) | No AE,<br>Exitus because of lymphoma progression |
| 7 | 59/M | 3 (splenic involvement) | Nodal TFH cell lymphoma, follicular type | 1 | DM | 6xCHOP (CR)<br>2xDHAP (SD)<br>14xBelinostat (CR) | No AE, Alive |
| 8 | 71/F | 4 (lung and pleural involvement) | PTCL, NOS | 2 | CHD, AF, Depression | Interferon (2 years) +RT (CR)<br>4x CHOP (PD)<br>1xBelinostat (NE) | No AE,<br>Exitus because of lymphoma progression |
| 9 | 78/F | 3 | AITL | 2 | HTN, DM | 6xCHOP (CR)<br>8x Gemsitabine +<br>Vinorelbine (CR)<br>2xBelinostat (PD)<br>11xLenalidomid (PD) | No AE,<br>Exitus because of<br><br>lymphoma progression |

Abbreviations: M, male; F, female; ALCL, anaplastic large cell lymphoma; TFH, T-follicular helper; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HTN, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; AF, atrial fibrillation; AE, adverse event; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; BV-CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisolone; ICE, ifosfamide, carboplatin, etoposide; BEAM, carmustine, etoposide, cytarabine, melphalan; RT, radiotherapy; DHAP, dexamethasone, cytarabine, cisplatin; BV-GDP, brentuximab vedotin, gemcitabine, dexamethasone, cisplatin; GEMOX, gemcitabine, oxaliplatin; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine, prednisolone; allo-SCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation.

tion was 65 years (range, 52 - 78). Four patients were male and five were female. PTCL subtypes consisted of five PTCL-NOS, two ALCL, one nodal TFH cell lymphoma follicular-type and one AITL. At the time of diagnosis, five patients were stage IV and four were stage III. According to the International Prognostic Index score, 2 patients had a score of 1, 4 had a score of 2, 2 had a score of 3, and 1 had a score of 4. Two patients had B symptoms at the time of diagnosis (Patient


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5, 8) and an Eastern Cooperative Oncology Group (ECOG) performance status of 1, except for two patients (both ECOG 2). EBV positivity was not detected in any of the patients by in situ hybridization. Patient demographics, clinical characteristics, treatment courses, and responses are summarized in Table 1.

One patient (Patient 7) had splenic involvement. Five patients (Patients 1, 2, 4, 6, 8) had extranodal diseases in one or more lung, pleura, bone, skin or gastric sites at diagnosis. None of the patients had bone marrow involvement.

All patients had received multiple prior therapies (median three lines; range: 3-4 lines) before belinostat, including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)-based chemotherapy, gemcitabine-based combinations (e.g., GEMOX [gemcitabine, oxaliplatin] and BV-GDP [brentuximab vedotin, gemcitabine, dexamethasone, cisplatin]), bendamustine-based regimens, or high-dose chemotherapy with stem cell transplantation. Despite these intensive approaches, patients were considered either relapsed or refractory at the time of belinostat initiation.

Of the nine patients, two (Patients 2, 6) underwent autologous stem cell transplantation (ASCT). Two additional patients (Patients 1, 5) achieved successful stem cell mobilization but were ultimately unable to proceed with ASCT due to disease progression or inadequate response. The remaining patients were deemed ineligible for transplantation. Among the two patients who had undergone ASCT, disease relapse required allogeneic stem cell transplantation (allo-SCT). In one case (Patient 2), belinostat served as bridging therapy prior to allo-SCT, whereas in the other (Patient 6) it was administered post-allo-SCT following relapse.

### *Belinostat treatment and response*

Belinostat was administered off-label in accordance with national regulations, as a monotherapy at a dose of 1000 mg/m$^2$ once daily on days 1–5 of a 21-day cycle. Of the nine R/R PTCL patients treated with belinostat, two (22.2%) achieved CR, one (11.1%) had SD, four (44.4%) developed PD and two (22.2%) died from lymphoma progression before a second cycle could be administered. The number of belinostat cycles ranged from 1 to 14 across the cohort. All patients were followed for a median of 37 months (range, 8-74 months). Response evaluations were performed using the Lugano criteria, primarily with PET-CT imaging after two cycles or earlier if clinically indicated. Among the nine patients, two achieved CR, one had SD, four showed PD, and two were not evaluable.

#### *Complete remission*

Two patients achieved CR (22.2%). One patient (Patient 2, ALCL, ALK-negative) achieved a complete response in all bone, skin, and nodal lesions following two cycles of belinostat. However, a new extramedullary lesion emerged in the right 7$^{th}$ costa. Radiotherapy was initiated for this lesion, and the third cycle of belinostat was administered concurrently. The patient achieved a complete response by the end of all treatment courses. Subsequently, she underwent allogeneic stem cell transplantation and remained alive and disease-free at the last follow-up. She is currently in the seventh month post-transplant and continues to receive belinostat as maintenance therapy. Another patient (Patient 7, nodal TFH lymphoma follicular type) experienced a prolonged CR after 14 cycles of belinostat and is also alive without progression.

#### *Stable disease*

One patient (Patient 6, PTCL-NOS; 11.1%) reached SD after four cycles. However, subsequent therapy with romidepsin was unsuccessful and the patient ultimately succumbed to disease progression.

#### *Progressive disease*

Four patients (Patients 1, 4, 5, 9; 44.4%) showed PD at the time of reassessment (after two cycles) or shortly thereafter. Two of these individuals (Patients 4, 9) died due to rapid disease progression, while the other two continued further lines of therapies (GEMOX and/or pralatrexate) with varying outcomes; both remain alive at data cutoff. Notably, response assessments conducted after two cycles of belinostat therapy revealed disease progression in extranodal sites that were not initially involved at the initiation of treatment. Specifically, Patient 1 exhibited bone marrow involvement, Patient 4 developed cutaneous involvement and Patient 5 demonstrated cerebrospinal fluid involvement.

#### *Not evaluable*

Two patients (Patients 3, 8; 22.2%) could not be formally evaluated for response, as both received only one cycle of belinostat and died from lymphoma progression before a follow-up assessment could be completed.

### *Survival and safety*

The median OS was 6.8 months (95% CI, 3.9 to 9.6; Figure 1). At last follow-up, 4 (Patients 1, 2, 5, 7) of the 9 patients (44%) were alive, and 2 of these continued belinostat therapy. Five patients (Patients 3, 4, 6, 8, 9) died from PTCL progression. The median PFS was 3.4 months (95% CI, 0.8 to 5.6; Figure 2). The six-month PFS rate, defined as the proportion of patients surviving without progression, was 25%. No patient experienced grade 3-4 adverse events related to belinostat, and there were no treatment discontinuations or dose reductions due to toxicity. All patients tolerated belinostat without requiring hospitalization for toxicity management.

## DISCUSSION

PTCL poses a major therapeutic challenge due to its limited treatment options and poor responses to conventional chemotherapy, particularly in the R/R setting [10–12].


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HDACs have recently gained attention as novel epigenetic targets in PTCL, as dysregulated acetylation and deacetylation processes can drive genomic instability and aberrant gene expression in this disease [5]. While salvage chemotherapy and ASCT remain standard approaches for R/R PTCL, their limited effectiveness highlights the continuous need for novel therapeutic approaches. First-line treatment for PTCL typically involves combination chemotherapy, most frequently the CHOP regimen or a CHOP-like protocol [13].

Promising findings were reported from a Phase I, single-arm trial evaluating belinostat combined with CHOP (Bel-CHOP) in newly diagnosed PTCL, yielding a 71% complete response rate and an 86% overall response rate (ORR) [8]. Although patients did not undergo consolidation with ASCT, the regimen was well tolerated, suggesting that earlier incorporation of HDAC inhibitors may confer clinical benefit for selected patient populations [8]. In the R/R setting, outcomes remain dismal; a retrospective analysis reported median PFS and OS of only 3.1 months and 5.5 months, respectively [12]. Against this setting, belinostat has shown promise, with the pivotal phase II BELIEF study leading to its accelerated FDA approval for R/R PTCL [7]. In that landmark trial, 120 evaluable patients achieved an ORR of 26% (CR, 11%), with a median duration of response of 13.6 months [7]. A later multicenter phase II study also confirmed the activity of belinostat in PTCL and cutaneous T-cell lymphoma (CTCL) but with somewhat lower response rates and shorter durations of response [14]. Overall, these observations suggest that belinostat may have clinical utility with an acceptable tolerability profile characterized mainly by grade 3–4 cytopenias.

While initial clinical trials have provided preliminary insights into efficacy of belinostat and safety, real-world data remain limited. The experience in the small, published Turkish cohort of 10 patients with R/R PTCL reported by Akdeniz et al. [15] reported a 50% objective response rate, with only one case of grade 3 neutropenia. More recently, the large-scale BELBRA study, conducted across 90 Brazilian lymphoma centers, examined belinostat in R/R PTCL and presented interim findings for 97 patients: an ORR of 45%, SD in 10%, and disease progression in 45% [9]. Notably, belinostat was generally well tolerated over an average of five treatment cycles, underscoring its potential as a salvage therapy for patients who have failed prior treatments [9].

Our own retrospective analysis included nine patients with R/R PTCL treated at three institutions, covering a spectrum of histopathological subtypes. All had advanced disease (Stage III–IV) and significant comorbidities. which limited their eligibility for transplantation. Despite these challenges, belinostat was administered as a third- to fifth-line treatment. According to national regulations, belinostat has not been approved as an early-line therapy and can only be used off-label in patients who have failed multiple prior treatments. Therefore, in our cohort, belinostat was administered in later lines of therapy. This reflects restrictions imposed by national health insurance coverage rather than physician preference. None of the patients experienced notable adverse events. Two patients (22.2%) achieved CR, including one who proceeded to allo-SCT and remains disease-free, and another who has sustained remission for 14 months on ongoing belinostat monotherapy. Four patients (44.4%) experienced disease progression by or soon after their second cycle, necessitating other salvage therapies; two subsequently died. An additional two patients received only a single cycle of belinostat and died from progression before response assessment. One patient achieved SD after four cycles but later succumbed to progression despite switching to another HDAC inhibitor. The median OS was 6.8 months and the median PFS was 3.4 months. The six-month PFS rate, defined as the proportion of patients surviving without progression, was 25%.

Another observation that was notable in our cases was the emergence of new extranodal involvement in four patients during belinostat treatment, despite positive responses in pre-existing nodal and extranodal lesions. We found no data on this topic in the literature. In general, these results reflect the aggressive nature of PTCL in an elderly and comorbid population and are consistent with previous literature indicating that belinostat may provide durable remission in a subgroup of patients but that early relapse is observed in many patients. There are primary or acquired resistance mechanisms to HDAC inhibitors. These mechanisms have been characterised in lymphoma models and may contribute to early progression. Resistance mechanisms include: reactivation of survival pathways such as PI3K/AKT and NF-κB, inadequate reprogramming due to epigenetic plasticity, increased anti-apoptotic signal transduction, and drug efflux via P-glycoprotein (ABCB1) [16,17]. Various combination strategies are being investigated to overcome resistance. In particular, the combination of HDAC inhibitors with hypomethylating agents (e.g., azacitidine + romidepsin) has been shown to achieve high response rates in TFH phenotypes in clinical trials and real-world data [18,19].

Impressively, none of our patients experienced serious adverse events or required therapy discontinuation due to toxicity, consistent with the safety profile observed in previous studies [7,9]. This finding is encouraging, although the small cohort size and retrospective data collection prevent definitive conclusions regarding tolerability.

Going forward, further research is needed to optimase the use of belinostat in PTCL. Exploring combination therapies -such as frontline Bel-CHOP or pairing belinostat with immunotherapies or other targeted agents- may offer improved effectiveness. Prospective multicenter or registry-based studies with larger sample sizes are essential to clarify belinostat's long-term safety, durability of response, and its most appropriate place in the treatment plan for both newly diagnosed and R/R PTCL.


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***Limitations***

Our findings should be interpreted with caution for several reasons. First and foremost the small sample size which limits statistical power and the capability to generalize the results. Second, the retrospective nature of our data gathering may introduce selection bias, given that each patient's treatment was at the discretion of their physician in everyday clinical practice. Third differences in follow-up intervals between the three centers, and two patients died before formal response evaluation, could potentially result in some outcomes being underestimated or missed. Lastly, the heterogeneity of PTCL subtypes and prior therapies, and the advanced stage of disease in most patients, may complicate direct comparison with clinical trial populations.

## CONCLUSION

In summary, the findings from our study underscore potential of belinostat inducing durable responses in a subset of heavily pretreated R/R PTCL patients. However, the small sample size and retrospective design emphasize the need for larger prospective trials to validate efficacy and optimize patient selection.

**Ethics Committee Approval:** Ethical approval was obtained from Istanbul Medipol University Ethics Committee (Date: 22-05-2025, Number: 580).

**Informed Consent:** Informed consent was not obtained due to the retrospective design of the study.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Author Contributions:** Materials and Data collection: G.A., E.Y., H.S.B., Ö.G.S.; Concept: S.Y.K.; Design: S.Y.K., L.K.; Data Collection or Processing: G.A., E.Y., S.M.; Analysis or Interpretation: S.Ç., S.Y.K., S.M.; Literature Search: L.K., S.Y.K.; Writing: S.Y.K., L.K.

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