Research paper

# Clinical outcomes of early-progressed follicular lymphoma in Korea: a multicenter, retrospective analysis

**Keywords**
follicular lymphoma, clinical outcomes, POD24

**Abstract**

Introduction
Due to the rarity of the disease, outcomes and treatment patterns of follicular lymphoma (FL) with POD24 (progressed within 24 months of diagnosis) in daily practice have been poorly defined in Korea.

Material and methods
Clinical data were retrospectively collected from patients who met the following criteria: 1) histologically confirmed diagnosis of FL; 2) POD24; 3) available medical records. The primary endpoint was overall survival (OS) from the first diagnosis of FL.

Results
From 2007 to 2019, 73 cases were eligible for analysis. The median age was 53 years, and 62 patients had received rituximab as induction treatment. POD24 was documented after a median duration of 11.6 months. For salvage treatment, platinum-based combinations (N=23) were the most used chemotherapy backbone followed by bendamustine- (N=15) and fludarabine-based combinations (N=12). The median progression-free survival (PFS) from the first progression was 23.7 months. The median OS was 128.9 months, with the 5-year OS rate being 75.2%. OS did not significantly differ by the reinduction regimen, the use of rituximab, or stem cell transplantation. When we compared these patients with 147 FL patients without POD24, the 5-year survival rate was significantly inferior in the current cohort (75.2% vs. 95.7%, $p < 0.001$).

Conclusions
The current study revealed that patients with early progressed FL have poor outcomes, in agreement with the findings of previous studies. Given that no existing treatment can overcome their poor prognosis, novel therapeutic approaches are needed.



**Explanation letter**

Dear Professor Maciej Banach.

We appreciate the interest that the editors and reviewers have taken in our manuscript and the constructive criticism they have given. We have addressed the major concerns of the reviewers and revised as recommended. In addition, as this article was reviewed by an English editing program, we attached a certificate for that.

We hope that you find our responses satisfactory and that the manuscript is now acceptable for publication. We also strongly believe that this article should be cited in many articles dealing with lymphoma near future.

Best regards,
Won Seog Kim, M.D., Ph.D.

Revision letter R2.docx

editing_certificate2.pdf

# Clinical outcomes of early-progressed follicular lymphoma in Korea: a multicenter, retrospective analysis

Running head: Early progressing follicular lymphoma

## ABSTRACT

**Introduction:** Due to the rarity of the disease, outcomes and treatment patterns of follicular lymphoma (FL) with POD24 (progressed within 24 months of diagnosis) in daily practice have been poorly defined in Korea.

**Material and Methods:** Clinical data were retrospectively collected from patients who met the following criteria: 1) histologically confirmed diagnosis of FL; 2) POD24; 3) available medical records. The primary endpoint was overall survival (OS) from the first diagnosis of FL.

**Results:** From 2007 to 2019, 73 cases were eligible for analysis. The median age was 53 years, and 62 patients had received rituximab as induction treatment. POD24 was documented after a median duration of 11.6 months. For salvage treatment, platinum-based combinations (N=23) were the most used chemotherapy backbone followed by bendamustine- (N=15) and fludarabine-based combinations (N=12). The median progression-free survival (PFS) from the first progression was 23.7 months. The median OS was 128.9 months, with the 5-year OS rate being 75.2%. OS did not significantly differ by the reinduction regimen, the use of rituximab, or stem cell transplantation. When we compared these patients with 147 FL patients without POD24, the 5-year survival rate was significantly inferior in the current cohort (75.2% vs. 95.7%, $p < 0.001$).

**Conclusions:** The current study revealed that patients with early progressed FL have poor outcomes, in agreement with the findings of previous studies. Given that no existing treatment can overcome their poor prognosis, novel therapeutic approaches are needed.



**Keywords:** follicular lymphoma, POD24, clinical outcomes

## INTRODUCTION

Follicular lymphoma (FL) is a subtype of B-cell non-Hodgkin's lymphoma characterized by t(14;18), which results in the overexpression of BCL2 and a nodular growth pattern. FL is a heterogeneous disease with a highly variable initial presentation that results in the use of a wide range of initial management strategies, including watchful waiting, radiation therapy, and immunotherapy with or without chemotherapy. Although FL is considered incurable, several novel agents represented by rituximab, bendamustine, or lenalidomide have successfully prolonged patients' survival [1-3]. Consequently, near-normal survival may be expected if a patient achieves durable remission by the frontline treatment [4].

In contrast, approximately 10%–20% of patients experience early treatment failure resulting in poor long-term survival. Several indices have been introduced to classify these patients, including event-free survival at 12/24 months [4], complete response at 30 months [5], Positron Emission Tomography-Computed Tomography (PET–CT) assessment after the frontline treatment [6], and progression of disease within 24 months of diagnosis (POD24) [7]. Because event-free survival at 12 months is more suitable for patients who were treated with non-aggressive initial therapy [4], and given that there are still different criteria for PET–CT response in lymphoma [8, 9], POD24 seems to be a more readily applicable surrogate marker for daily practice.

FL is the most common indolent lymphoma, accounting for 10%–20% of all lymphomas in the Western world [10, 11]. However, its incidence is much lower in Asians and their descendants [12, 13]. In addition to the paucity of this disease, the low incidence of early treatment failure has also contributed to limited data for Asian FL patients with POD24.

Therefore, we have carried out a multicenter, retrospective analysis to address this uncommon but significant issue.

## MATERIAL AND METHODS

### *Patients*

The inclusion criteria were as follows: 1) histologically confirmed diagnosis of FL grades 1, 2, or 3A; 2) documented progression within 24 months after the initiation of induction chemotherapy; and 3) available medical records, including clinicopathologic characteristics and clinical outcomes. Patients with follicular lymphoma grade 3B or patients with incomplete medical records were excluded from the analysis. Patient medical records were collected; they included age; sex; histologic grade; the Eastern Cooperative Oncology Group Performance Status (ECOG-PS); stage; number of nodal involvements; largest tumor diameter; laboratory findings, including complete blood count, serum lactate dehydrogenase (LDH), and β2-microglobulin; treatment modalities; and treatment outcomes.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed-consent exemptions were approved by the institutional review boards of each institute.



### *Statistical analysis*

The primary endpoint of the analysis was overall survival 1 (OS1), which was calculated from the date of the first FL diagnosis to the date of death. OS2 was calculated from the date of initiation of the second induction treatment to the date of death. PFS 1, 2, and 3 were calculated from the initiation of the first, second, and third induction treatments to the date of progression or death for each treatment. These survival analyses were performed using the

Kaplan–Meier method and compared using log-rank tests. Response was defined by Lugano classification [8] using the neck, chest, and abdomen-pelvis CT taken every 3 cycles of treatment during the induction with or without maintenance therapy and was compared using Pearson's $\chi^2$ tests. For all statistical analyses, $p < 0.05$ was considered significant, and the analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### *Patient characteristics and outcomes by induction treatment*

From 2007 to 2019, a total of 73 patients were eligible for inclusion in the study (Supplementary figure 1). At the time of initial treatment, the median age of the patients was 53 years (interquartile range (IQR), 43–60), and 45 patients (61.6%) were male. Serum β2-microglobulin levels were recorded in 53 patients, and the median value was 2.1 mg/L (IQR, 1.58–3.01 mg/L). The median diameter of the largest tumor was 5.1 cm (IQR, 3.4–9.6 cm). The details are described in Table I.

Regarding induction therapy, 62 patients (84.9%) had received rituximab, and 11 patients (15.1%) had not. CVP (cyclophosphamide, vincristine, and prednisone) was the most prevalent chemotherapy backbone (*n*=41, 56.2%), followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, *n*=26, 35.6%), fludarabine-based regimens (*n*=4, 5.5%), and bendamustine-based regimens (*n*=2, 2.7%). Forty-four patients (60.3%) received subsequent maintenance treatment. In terms of the best response during induction with or without maintenance therapy, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were noted in 32 (43.8%), 34 (43.8%), 3 (4.1%), and 6 (8.2%) patients, respectively. The median PFS1 was 11.6 months (95% CI, 9.8–13.4). The use of rituximab, the type of the chemotherapy backbone, whether patients had received maintenance treatment, and the FLIPI-1 risk group did not impact PFS1. The details are described in Table II.

### *Clinical outcomes by salvage treatment*

At the time of progression or relapse, 34 patients were rebiopsied, and except for three cases of large cell transformation (8.8%), all cases were classified as FL recurrences. The ECOG-PS were 0–1 in 67 patients (91.8%) and 2–4 in 6 patients (8.2%). Hemoglobin less than 12 g/dL was noted in 15 patients (20.5%), and elevated serum LDH was noted in 23 patients (31.5%). Twenty-six patients (35.6%) had five or more areas of nodal involvement, and the median diameter of the largest tumor was 4.8 cm (IQR, 2.0–7.1 cm).

Except for two patients who were only observed, 71 patients received salvage treatment. Rituximab was administered to 19 patients (26.0%), of whom 17 patients had received rituximab as the initial treatment. Platinum-based combinations, including ICE (ifosfamide, carboplatine, and etoposide) (*n*=10); ESHAP (etoposide, solu-medrol, cytarabine, and cisplatin) (*n*=10); and DHAP (dexamethasone, cytarabine, and cisplatin) (*n*=3), were the most frequently applied regimens. Bendamustine with (*n*=9) or without rituximab (*n*=6) were the second-most frequently used treatments. Fludarabine-based combinations, including FND (fludarabine, mitoxantrone, and dexamethasone) (*n*=9) and FMC (fludarabine, mitoxantrone, and cyclophosphamide) (*n*=3), were the third-most frequently used treatments. The other patients were treated with CHOP (*n*=5), CVP (*n*=4), or rituximab monotherapy (*n*=5).

Treatment response was assessed in 71 patients. Because PR and CR were noted in 23 (31.5%) and 28 patients (38.4%), respectively, the overall response rate (ORR) was 69.9%. The estimated median PFS2 was 23.7 months (95% CI, 7.8–39.6). None of the following factors were associated with PFS2: age, serum LDH, number of nodal involvements, tumor size, or hemoglobin. Although patients treated with rituximab exhibited prolonged PFS2, the difference was not statistically significant (31.4 months vs. 22.9 months, p=0.432). Similarly,

when the chemotherapy backbones was categorized into CHOP, bendamustine-based combinations, platinum-based combinations, and fludarabine-based treatments, there were no significant differences in survival (p=0.957) (FIGURE 1A) and ORR (p=0.568). The details are described in Table III. The second salvage treatment was administered to 32 patients, and the estimated median PFS3 was 9.0 months (5.0–13.0).

***Stem cell transplantation***

A total of 15 patients received hematopoietic stem cell transplantation. The median age of the patients (50 years, IQR 39–55) was not significantly different from those who did not receive transplantation (53, IQR 44–63). Autologous stem cell transplantation (ASCT) was carried out in 12 patients. Of these, only 1 patient received ASCT after the second salvage treatment (bendamustine–ESHAP), whereas the other 11 patients received ASCT after the first salvage treatment (9 platinum-based combinations and 2 bendamustine-based combinations). Allogeneic stem cell transplantation (AlloSCT) was carried out in 3 patients. Of these, 2 patients received AlloSCT after 2 salvage treatments (ICE–DHAP and ICE–bendamustine), whereas 1 patient received AlloSCT after 6 lines of treatment.

The impact of ASCT on PFS2 was evaluated in 11 patients who received ASCT after the first salvage treatment and 40 patients who did not receive ASCT after the achievement of at least one PR from the first salvage treatment. The PFS2 did not reach the median value in any of the patients and was not significantly different between the two groups (p=0.982) (**FIGURE 1B**). The 2-year PFS2 rates were 63.5% (±16.9%) in the ASCT group and 60.8% (±8.4%) in the no-ASCT group.

***Overall survival***

With a median follow-up duration of 68.0 months (95% CI, 54.5–81.5), the estimated median OS1 was 128.9 months, and the five-year OS1 rate was 75.2% (±5.8%). The five-year OS1 rate of different FLIPI-1 risk groups was not significantly different: 82.5% (±11.5%) for the low-risk group, 79.3% (±9.3%) for the intermediate-risk group, and 70.6% (±8.4%) for the high-risk group (p=0.376). Moreover, the use of rituximab, the type of induction chemotherapy, and stem cell transplantation did not impact five-year OS1 rates. The median OS2 was 108.0 months, and the five-year OS2 rate was 67.1% (±7.2%). The two-year OS2 rates were 90.9% (±8.7%) for the ASCT group and 91.0% (±5.0%) for the no-ASCT group.

Next, we compared the OS1 rate of the current cohort and our historical cohort for FL without POD24. Among 343 patients with FL from 1993 to 2013 [14], 147 patients who had not experienced POD24 were included in the analysis. The median age of the 147 patients was 52 years (IQR, 41–61), and 82 patients (55.8%) were male. Eighty (54.4%), 35 (23.8%), and 32 (21.8%) patients were classified into low-, intermediate, and high-risk FLIPI-1 groups, respectively. CVP, CHOP, R–CVP, and R–CHOP were administered in 17 (11.6%), 47 (32.0%), 46 (31.3%), and 31 (21.1%) patients, respectively. The five-year OS1 rate of the patients without POD24 was 95.7% (±1.9%), which was significantly higher than those of patients with POD24 in the current study (p<0.001) (**FIGURE 2**). The characteristics of the two groups are provided in supplementary table I.

## DISCUSSION

In the current study, we analyzed 73 patients with FL and POD24. Once POD24 occurred, the median PFS2 achieved by salvage treatment was 23.7 months (95% CI, 7.8–39.6), and no single treatment, including stem cell transplantation, was shown to be superior for improving PFS2. The five-year OS1 rate was 75.2%, which was significantly lower than that of patients not experiencing POD24 (95.7%).

Although the median OS of FL patients reaches nearly 20 years, a small proportion of patients will have early treatment failure and POD24 is one of the most widely validated endpoints. Casulo et al. [7] analyzed 588 patients with FL who were treated with frontline R-CHOP and found that 110 patients (18.7%) experienced POD24 and had an inferior five-year OS rate (50% vs. 90%). In the PRIMA trial, early progression was noted in approximately 24.2% of patients and associated with inferior OS (five-year OS rate of 63% vs. 92%) [15, 16]. Of the 1202 patients in the GALLIUM trial, 155 patients (16.3%) treated with R-chemo and 57 patients (9.5%) treated with G-chemo experienced POD24 [17]. The two-year OS rates were 82.4% and 98.2% in the POD24 and non-POD24 groups, respectively. In a study by Jurinovic et al., mutations of 7 genes, including *ARID1A, CARD11, CREBBP, EP300, EZH2, FOXO1*, and *MEF2B*, at the time of diagnosis could predict POD24 and the significantly worse overall survival [18]. Collectively, approximately 20% of FL patients receiving frontline treatment will have POD24, depending on the treatment, and their expected survival is significantly worse. In accordance with these studies in Western populations, we found that patients with POD24 were associated with significantly inferior survival rates (75.2% vs. 95.7%, $p<0.0001$).

Appropriate management of patients with POD24 remains elusive. Because most patients are now treated with rituximab-based therapy, obinutuzumab—a novel anti-CD20 monoclonal antibody—may be useful for overcoming rituximab resistance. In the phase III GADOLIN trial, 413 rituximab-refractory FL patients were allocated to either the obinutuzumab plus bendamustine group or to the bendamustine alone group [19]. The five-year OS rate for the obinutuzumab plus bendamustine group was over 60%, which was significantly higher than that of the bendamustine-alone group (p=0.027). In the phase II GALEN trial, 89 patients with rituximab-failed FL were treated with obinutuzumab plus lenalidomide [20]. At two years, the best ORR was 79%, and the PFS rate was 65%. Notably, these numbers were not significantly different between POD24 patients (*n*=24) and the non-POD24 patients (*n*=62), suggesting that the combination treatment may overcome the poor outcomes of POD24 patients.

The role of ASCT has been evaluated in several retrospective analyses. A total of 349 POD24 patients were analyzed (no ASCT, 174; ASCT, 175) in collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study (NCLS) [21]. Overall, there was no difference in OS between the two groups because both uni- and multivariate analyses failed to discriminate OS. Although the study did suggest that early ASCT within one year was associated with improved OS (p=0.05), refractoriness of the subsequent salvage treatment, which could have confounded the outcomes of the no-ASCT group, was not considered. In this regard, a German study may provide some information [22]. In this study, 113 patients who experienced POD within 24 months, and 49 patients who experienced POD after 24 months were analyzed. In the POD24

group, 52 patients had received ASCT, and 61 patients had not. A significant survival benefit was associated with ASCT, with a five-year OS2 rate of 77% vs. 59% (p=0.031), which was comparable to those who developed POD after 24 months. However, the five-year OS2 rate was not significantly different (p=0.35) compared with 36 patients without salvage treatment failure.

The current study showed similar findings. When we compared 11 patients who had received ASCT with 40 patients not receiving ASCT without salvage treatment failure, the PFS and OS were not significantly different: the two-year PFS rates of both groups were ~60%, and the five-year OS rates were ~90%. Thus, it is unclear whether POD24 patients may benefit from ASCT in terms of survival, especially in the era of novel agents. In fact, the two-year OS rate of POD24 patients in the GALEN trial was over 80%, similar to the two previously mentioned retrospective studies examining ASCT. In the future, it may be beneficial to provide chimeric antigen receptor T-cell therapy to these patients at risk. In the ZUMA-5 trial, axi-cel demonstrated a CR rate of 71.9% and ORR of 93.0% in 57 patients with POD24 [23]. Due to its retrospective nature, our study has several limitations, including a lack of full data for serum β2-microglobulin and bone marrow involvement, which are newly introduced prognostic markers. The frontline and second-line regimens are heterogeneous, which hinders the discovery of optimal treatments for POD24 patients. However, other than obinutuzumab plus bendamustine, no treatments have been found to prolong OS. Second, due to the limited availability of novel agents, patients have been treated with conventional cytotoxic agents. For example, even rituximab was not administered in nine patients (12.3%) during their treatment. Because the use of rituximab does impacts survival [1], this undertreatment may

have influenced patients' outcomes. However, when we analyzed the PFS1 ($p = 0.896$), PFS2 ($p = 0.740$), OS1 ($p = 0.411$), and OS2 ($p = 0.413$), there was no significant difference between 59 patients who were treated with R plus chemotherapy and the 14 patients who were not, which could be attributed to the small number of the patients in the subgroup. Third, re-biopsy was performed in only 34 patients. Except 3 cases of large cell transformation, additional immunohistochemical staining or genetic study was not carried out. Given that POD24 is frequently accompanied by transformation [17, 24], re-biopsy could be a crucial factor in determining treatment. Fourth, PET–CT imaging was not assessed.

## CONCLUSION

Our analysis of the 73 FL patients experiencing POD24 revealed that they have poor outcomes, in agreement with the findings of previous studies. Given that no existing treatment could overcome their poor prognosis, novel therapeutic approaches are needed.

# REFERENCES


1. Armitage JO, Longo DL. Is watch and wait still acceptable for patients with low-grade follicular lymphoma? Blood 2016; 127: 2804-8.
2. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381: 1203-10.
3. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med 2018; 379: 934-47.
4. Maurer MJ, Bachy E, Ghesquières H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol 2016; 91: 1096-101.
5. Shi Q, Flowers CR, Hiddemann W, et al. Thirty-Month Complete Response as a Surrogate End Point in First-Line Follicular Lymphoma Therapy: An Individual Patient-Level Analysis of Multiple Randomized Trials. J Clin Oncol 2017; 35: 552-60.
6. Trotman J, Barrington SF, Belada D, et al. Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): secondary analysis of a randomised, phase 3 trial. Lancet Oncol 2018; 19: 1530-42.
7. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol 2015; 33: 2516-22.
8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32: 3059-68.
9. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007; 25: 571-8.
10. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016; 66: 443-59.
11. Mounier M, Bossard N, Remontet L, et al. Changes in dynamics of excess mortality rates and net survival after diagnosis of follicular lymphoma or diffuse large B-cell lymphoma: comparison between European population-based data (EUROCARE-5). Lancet Haematol 2015; 2: e481-91.

12. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, Kruczek K, Smith SM, Evens AM. The impact of race, age, and sex in follicular lymphoma: A comprehensive SEER analysis across consecutive treatment eras. Am J Hematol 2014; 89: 633-8.
13. Lee H, Park HJ, Park EH, et al. Nationwide Statistical Analysis of Lymphoid Malignancies in Korea. Cancer Res Treat 2018; 50: 222-38.
14. Cho SH, Suh C, Do YR, et al. Clinical Features and Survival of Patients With Follicular Lymphoma in Korea. Clin Lymphoma Myeloma Leuk 2016; 16: 197-202.
15. Bachy E, Seymour JF, Feugier P, et al. Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients With Follicular Lymphoma: Long-Term Results of the PRIMA Study. J Clin Oncol 2019; 37: 2815-24.
16. Bachy E, Maurer MJ, Habermann TM, et al. A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy. Blood 2018; 132: 49-58.
17. Seymour JF, Marcus R, Davies A, et al. Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression. Haematologica 2019; 104: 1202-8.
18. Jurinovic V, Kridel R, Staiger AM, et al. Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy. Blood 2016; 128: 1112-20.
19. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol 2018; 36: 2259-66.
20. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol 2019; 6: e429-e37.
21. Casulo C, Friedberg JW, Ahn KW, et al. Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant 2018; 24: 1163-71.
22. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant 2018; 24: 1172-9.
23. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022; 23: 91-103.

24. Freeman CL, Kridel R, Moccia AA, et al. Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma. Blood 2019; 134: 761-4.

## FIGURE LEGENDS

Figure 1. Progression-free survival-2. according to A, backbone salvage chemotherapy; B, after achieving a partial or complete response, followed by stem cell transplantation or not.

Figure 2. Overall survival-1 for patients with POD24 versus those without POD24 (five-year OS1 rate 75.2% vs. 95.7%, $p<0.001$).

Supplementary figure 1. Flow chart for patients inclusion.

Table I. Baseline characteristics at induction treatment (*n*=73)

| **Characteristic** | ***n* (%)** |
|---|---|
| Age, median (range) | 53 (28–83) |
| Age≤60 years | 55 (75.3) |
| Age>60 years | 18 (24.7) |
| Sex | |
| Male | 45 (61.6) |
| Female | 28 (38.4) |
| ECOG-PS | |
| 0–1 | 68 (93.2) |
| 2–4 | 5 (6.8) |
| WHO histologic grade | |
| 1 | 27 (39.7) |
| 2 | 22 (32.3) |
| 3A | 19 (27.9) |
| Not specified | 5 (6.8) |
| Stage | |
| I, II | 11 (14.0) |
| III, IV | 62 (86.0) |
| Serum LDH | |
| Normal | 48 (65.8) |
| Elevated | 25 (34.2) |
| B Symptom (*n*=70) | |
| Present | 14 (20.0) |
| Absent | 56 (80.0) |
| Bone marrow (*n*=72) | |
| Involved | 41 (56.9) |
| Not involved | 31 (43.1) |
| Splenomegaly | |
| Present | 30 (41.1) |
| Absent | 43 (58.9) |
| Largest tumor size (cm), median (range) | 5.1 (1.2–23.0) |
| Effusion | |
| Present | 16 (21.9) |
| Absent | 57 (78.1) |
| Number of involved nodal area(s) | |
| 0–4 | 26 (35.6) |
| 5 or more | 47 (64.4) |
| Serum β2-microglubulin (*n*=53), median (range) | 2.1 (0.74–9.67) |
| FLIPI-1 risk group | |
| Low-risk | 14 (19.2) |
| Intermediate-risk | 24 (32.9) |
| High-risk | 35 (47.9) |

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; FLIPI, follicular lymphoma international prognostic index

Table II. Induction treatments and their outcomes

| Characteristic | *n* (%) |
|---|---|
| Rituximab | |
| Used | 62 (84.9) |
| Not used | 11 (24.7) |
| Backbone regimen | |
| CVP | 41 (56.2) |
| CHOP | 26 (9.8) |
| Rituximab monotherapy | 3 (4.1) |
| Bendamustine | 2 (2.7) |
| FMC | 1 (1.4) |
| Treatment cycle, median (range) | 6 (1–8) |
| Maintenance treatment | |
| Used | 44 (60.3) |
| Not used | 29 (39.7) |
| Best response | |
| Complete response | 32 (43.8) |
| Partial response | 32 (43.8) |
| Stable disease | 3 (4.1) |
| Progressive disease | 6 (8.2) |
| PFS1 (months), median (95% CI) | 11.6 (9.8–13.4) |
| PFS1 by induction regimen (months), median (95% CI) | |
| CVP (*n*=8) | 7.8 (7.5–8.1) |
| R-CVP (*n*=33) | 14.0 (11.6–16.4) |
| CHOP (*n*=3) | 14.2 (7.0–21.4) |
| R-CHOP (*n*=23) | 11.4 (9.2–13.6) |
| PFS by maintenance treatment | |
| Used | 10.0 (6.9–13.1) |
| Not used | 13.0 (10.7–15.3) |
| PFS1 by FLIPI-1 risk group, median (95% CI) | |
| Low-risk | 15.5 (12.9–18.1) |
| Intermediate-risk | 11.9 (10.0–13.8) |
| High-risk | 10.1 (8.1–12.1) |

CVP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FMC, fludarabine, mitoxantrone, and cyclophosphamide; PFS, progression-free survival, FLIPI, follicular lymphoma international prognostic index

Table III. First salvage treatment and their outcomes

| **Characteristic** | ***n* (%)** | |
|---|---|---|
| Rituximab | | |
| Used | 19 (26.0) | |
| Not used | 54 (74.0) | |
| Backbone regimen | | |
| Platinum-based combinations | 23 (31.5) | |
| Bendamustine-based combinations | 15 (20.5) | |
| Fludarabine-based combination | 12 (16.4) | |
| Rituximab monotherapy | 5 (6.8) | |
| CHOP | 5 (6.8) | |
| CVP | 4 (5.5) | |
| Vorinostat | 3 (4.1) | |
| Observation | 2 (2.7) | |
| Others | 4 (5.5) | |
| Best response (*n*=71) | | |
| Complete response | 28 (38.4) | |
| Partial response | 23 (31.5) | |
| Overall response by backbone regimen | | p=0.568 |
| Platinum-based combinations | 16/23 (69.6) | |
| Bendamustine-based combinations | 13/15 (86.7) | |
| Fludarabine-based combination | 9/12 (75.0) | |
| CHOP | 3/5 (60.0) | |
| PFS2 (months), median (95% CI) | 23.7 (7.8–39.6) | |
| PFS2 by use of rituximab (months), median (95% CI) | | |
| Used | 31.4 (N/A) | |
| Not used | 22.9 (13.9–31.9) | |
| PFS2 by backbone regimen (months), median (95% CI) | | p=0.957 |
| Platinum-based combinations | Not reached | |
| Bendamustine-based combinations | 19.1 (18.1–20.1) | |
| Fludarabine-based combination | 26.0 (0.0–52.5) | |
| CHOP | 22.9 (0.0–54.9) | |



CVP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone;

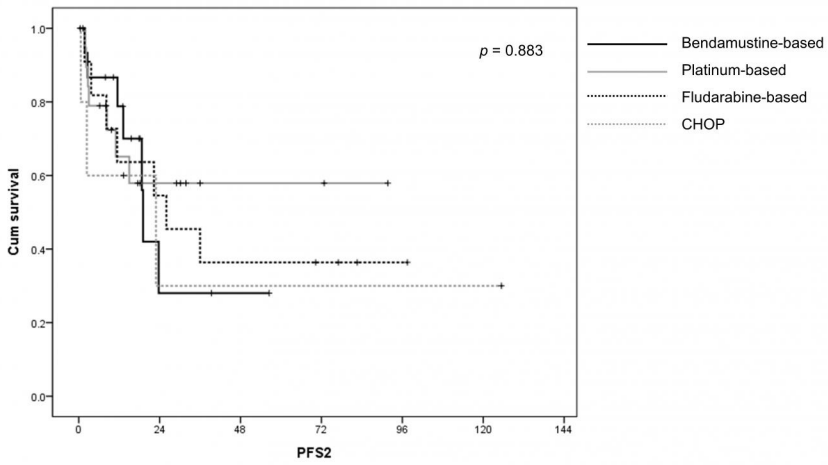
PFS, progression-free survival

Supplementary Table I. Comparison of patients with POD24 (*n*=73) and patients without POD24 (*n*=147) from the historical cohort at the time of diagnosis (compared by Pearson's $\chi^2$ tests)

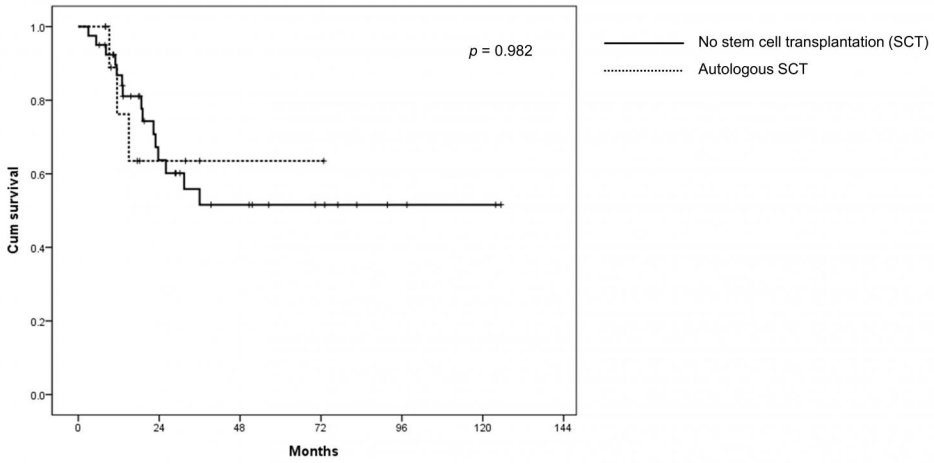
| Characteristic | With POD24 | Without POD24 | p |
|---|---|---|---|
| Age, median (range) | 53 (28 – 83) | 52 (16 – 80) | 0.848 |
| Age≤60 years | 55 (75.3) | 109 (74.1) | |
| Age>60 years | 18 (24.7) | 38 (25.9) | |
| Sex, *n* (%) | | | 0.407 |
| Male | 45 (61.6) | 82 (55.8) | |
| Female | 28 (38.4) | 65 (44.2) | |
| ECOG-PS, *n* (%) | | | 0.248 |
| 0–1 | 68 (93.2) | 142 (96.6) | |
| 2–4 | 5 (6.8) | 5 (3.4) | |
| **WHO histologic grade, *n* (%)** | | | 0.226 |
| **1** | **27 (39.7)** | **38 (25.9)** | |
| **2** | **22 (32.3)** | **36 (24.5)** | |
| **3A** | **19 (27.9)** | **55 (37.4)** | |
| **3B** | **0 (0.0)** | **8 (5.4)** | |
| **Not specified** | **5 (6.8)** | **10 (6.8)** | |
| Stage, *n* (%) | | | <0.001 |
| I, II | 11 (14.0) | 68 (46.3) | |
| III, IV | 62 (86.0) | 79 (53.7) | |
| Serum LDH, *n* (%) | | | 0.128 |
| **Normal** | **48 (65.8)** | **111 (75.5)** | |
| Elevated | 25 (34.2) | 36 (24.5) | |
| B Symptom, *n* (%) | *n* = 70 | *n* = 143 | 0.009 |
| Present | 14 (20.0) | 15 (10.5) | |
| Absent | 56 (80.0) | 128 (89.5) | |
| Bone marrow, *n* (%) | *n* = 72 | *n* = 145 | <0.001 |
| Involved | 41 (56.9) | 31 (21.4) | |
| Not involved | 31 (43.1) | 114 (78.6) | |
| Number of involved nodal areas, *n* (%) | | | <0.001 |
| 0–4 | 26 (35.6) | 108 (73.5) | |
| 5 or more | 47 (64.4) | 39 (26.5) | |
| Induction treatment, *n* (%) | | | |
| R-CHOP | 23 (31.5) | 31 (21.1) | |
| R-CVP | 33 (45.2) | 46 (31.3) | |
| CHOP | 3 (4.1) | 47 (32.0) | |
| CVP | 8 (11.0) | 17 (11.6) | |
| FLIPI-1 risk group, *n* (%) | | | <0.001 |
| Low-risk | 14 (19.2) | 80 (54.4) | |
| Intermediate-risk | 24 (32.9) | 35 (23.8) | |
| High-risk | 35 (47.9) | 32 (21.8) | |

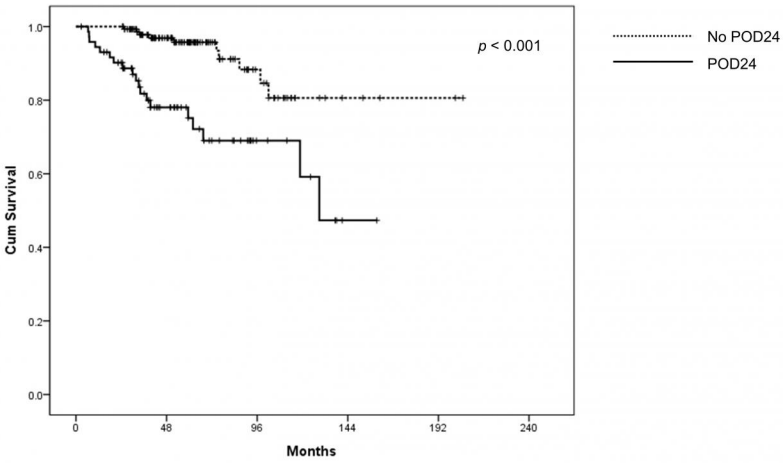
ECOG PS, Eastern Cooperative Oncology Group performance status; WHO, World Health Organization; LDH, lactate dehydrogenase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; FLIPI, follicular lymphoma international prognostic index

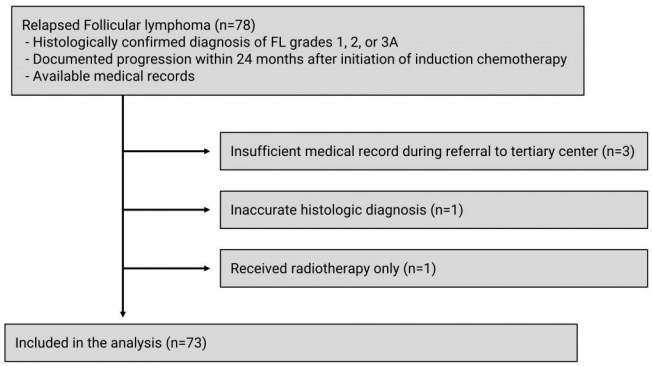
A


p = 0.883
Bendamustine-based
Platinum-based
Fludarabine-based
CHOP
Cum survival
1.0
0.8
0.6
0.4
0.2
0.0
0
24
48
72
96
120
144
PFS2

**B**


1.0
0.8
0.6
0.4
0.2
0.0
Cum survival
p = 0.982
0
24
48
72
96
120
144
Months
No stem cell transplantation (SCT)
Autologous SCT


1.0
0.8
0.6
0.4
0.2
0.0
Cum Survival
0
48
96
144
192
240
Months
p < 0.001
No POD24
POD24




Flow chart for patients inclusion