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LETTER

Early progression beyond first-line chemoimmunotherapy in follicular lymphoma: Insights from a Fondazione Italiana Linfoma (FIL) study

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Follicular lymphoma (FL) is the most common indolent B-cell lymphoma.[1,2] While most patients with FL have a truly indolent clinical course with standard therapy (ICT),[3] one out five patients experience early relapse or progression (R/P), leading to notably poor outcomes with a 5-year overall survival (OS) of only 60%.[4,5] These so-called POD24 patients usually show aggressive behavior mainly due to histological transformation (HT) and emergent chemo-resistant disease.[6–13] However, not all POD24 patients face unfavorable outcomes, underscoring the need for extensive real-life data to elucidate FL behavior after the first relapse.[14] We conducted a retrospective multicenter study to assess the outcomes of a real-world cohort of FL patients at their first relapse. Patients with grade 1 to 3a FL who experienced their first R/P after first-line standard ICT between 2002 and 2017 were eligible. Of note, patients with HT at first relapse were excluded in order to describe a homogeneous FL population. Clinical and laboratory features were documented at diagnosis and the first and second R/P, with optional histological confirmation details of first R/P. The study received approval from

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ethic committees at each participating institution, and all patients provided informed consent. The primary endpoint was progression-free survival from first relapse (index date; PFS2). The secondary endpoint was survival after the first relapse (SAR). POD24r was defined as disease R/P within 24 months after the start of the first salvage therapy. The endpoint definition is reported in the supplementary material.

The initial cohort included 175 patients, enrolled by 16 centers of Fondazione Italiana Linfomi (FIL), and 155 were confirmed eligible (Supporting Information S1: Figure 1). The key characteristics of patients both at diagnosis and at index date are shown in Table 1. Even if a biopsy was not mandatory, a pathology report consistent with FL at index date was available for 117 cases. Regarding initial therapy, most of the patients were treated with the R-CHOP regimen (98, 63%), and rituximab maintenance was administered in 59 cases. POD24 was documented in 59 patients (38%); 141 patients received a second-line therapy consisting mainly of R-Bendamustine and platinum-based therapy (41; 29%, and 37; 26%, respectively) (Table 1).

After a median follow-up of 48 months from the index date (interquartile range [IQR]: 25–68 months), 64 patients experienced a subsequent relapse or progression with a median PFS2 of 55 months (95% confidence interval [CI], 44–83 months). 4-year PFS2 rates was 55% (95% CI: 46%–63%). In univariate analysis, only male sex, increased beta-2-microglobulin (β2-M) levels at index date, and POD24 predicted lower PFS rates (Supporting Information S1: Table 1 and Supporting Information S1: Figure 2). In multivariate analysis, only POD24 retained predictive capacity for PFS2, with a borderline correlation for increased β2-M levels at relapse (Supporting Information S1: Table 1).

Median SAR was not reached, and 4-year SAR rate was 89% (95% CI: 82%–94%). Among variables analyzed at index date (Supporting Information S1: Table 2), only patients older than 60 years and those with POD24 showed a higher risk of shorter SAR. 4-year SAR rates for POD24 and non-POD24 cases were 81% (95% CI: 66–90) and 95% (95% CI: 87–98), respectively (hazard ratio [HR]: 3.4; 95% CI: 1.16–9.95: Supporting Information S1: Figure 3).

Among 64 patients who experienced a second R/P, 36 relapsed within 24 months from the index date and were identified as POD24r. Except for being POD24 and for the use of maintenance after first-line therapy, none of the variables were associated with POD24r risk (Supporting Information S1: Table 3).

We then analyzed the effect of POD24r on survival, applying the method originally defined by Casulo et al.[6] for newly diagnosed patients and using SAR as endpoint. Patients experiencing POD24r demonstrated lower SAR rates, with an HR of 19.4 compared to non-POD24r cases (95% CI: 4.2–89.7; $p < 0.001$) (Figure 1A).

Given that not all POD24 experienced poor outcomes, we analyzed the interplay between POD24 and POD24r, defining four patient groups (Supporting Information S1: Table 4). The first group, with neither POD24 nor POD24r, served as reference (63 cases, 50%). The second group had POD24 but no POD24r (27 cases, 21%), the third had no POD24 but had POD24r (10 cases, 8%), and the fourth group had both POD24 and POD24r (26 cases, 21%). Figure 1B depicts a Kaplan–Meier survival analysis evaluating the probability of SAR over time among four distinct patient groups, characterized by their POD24/POD24r status.

When SAR was analyzed in a multivariable analysis, we confirmed a significantly higher risk of shorter SAR only for groups 3 and 4 (HR = 26.7, 95% CI: 5.52–284; $p < 0.001$), while group 2 showed a nonsignificant increase in the risk of death (HR = 3.72, 95% CI: 0.49–40.8; $p = 0.194$).

Overall, this study highlights the high heterogeneity of the outcomes of patients with FL who experience a first relapse confirming

TABLE 1 Main characteristics of 155 follicular lymphoma patients evaluated at initial diagnosis and at the time of first relapse/progression (index date).

At diagnosis	Missing	N (%)
Gender		
Male	-	67 (43)
Age		
Years (median, range)	-	58 (30–82)
FLIPI	12	
Low-risk		25 (18)
Intermediate-risk		49 (34)
High-risk		68 (48)
First-line therapy	-	
R-CHOP		98 (63)
R-CVP		20 (13)
R-Fludarabine based		32 (21)
R-Bendamustine		3 (2)
Other		2 (1)
Response to first line	2	
CR		119 (77)
PR		31 (20)
SD/PD		3 (2)
First-line rituximab maintenance		59 (38)
At first relapse (index date)		
Age	-	
Years (median, range)		62 (33–86)
>60	-	82 (53)
Stage III–IV	3	103 (67)
LDH > UNL	13	38 (27)
β2-M > UNL	35	54 (45)
Hemoglobin <120 g/L	6	16 (11)
Number of nodal sites >3	1	66 (50)
POD24	-	59 (38)
Second-line therapy	14[a]	
Chemotherapy		2 (1)
Immunochemotherapy		112 (79)
Immunotherapy single agent		15 (11)
Local therapy (RT)		7 (5)
Novel agents		5 (4)
Response to second-line therapy	18[a]	
CR		97 (69)
PR		27(19)
SD/PD		13 (9.2)
ASCT (consolidation to 2nd line therapy)	14[a]	49 (35)
Rituximab maintenance after second-line	14[a]	65 (46)

Abbreviations: β2-M, β2 microglobulin; ASCT, autologous stem cell transplant; FLIPI, Follicular Lymphoma International prognostic index; LDH, lactate dehydrogenase; POD24, progression of disease ≤24 months from start of first-line therapy; RT, radiotherapy; UNL, upper normal level.

[a]14 patients who were only observed without any active treatment at index date were considered as missing for the assessment of second-line therapy.

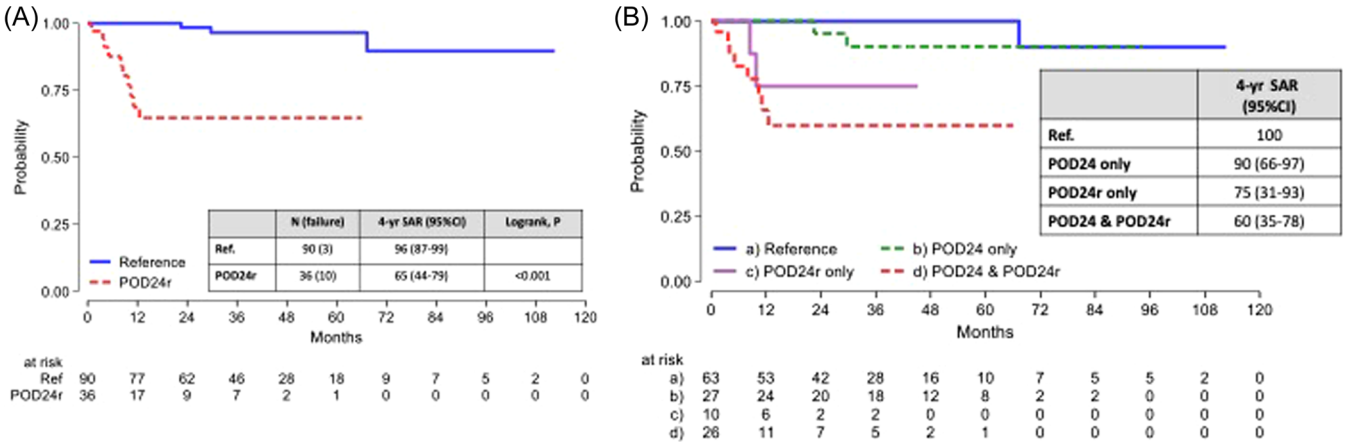

FIGURE 1 **Survival after relapse (SAR) stratified by early progression of disease (POD) after second-line therapy, that is, within 24 months (POD24r) or longer than 24 months (Reference group) (A), and by combining POD24 and POD24r (B)**. The combinations resulted in 4 groups, that is, those with neither POD24 nor POD24r (Reference group), cases with only POD24 or POD24r, and cases with both POD24 and POD24r.

that among evaluated characteristics, the duration of response to first (POD24) and second-line (POD24r) therapy are the strongest predictors of survival.

Few studies have been conducted to describe the outcome of real-life relapsed refractory FL patients, and most of the available data sets are referred to patients treated with at least two lines of therapy.[15,16] Our study was specifically defined to analyze the population of patients who experienced a first relapse after initial immunochemotherapy. Unfortunately, none of the clinical features collected at the time of initial diagnosis and study inclusion (first relapse) were useful for predicting the risk of subsequent progression or death. This result may be attributed to the small sample size, highlighting the need for more accurate biomarkers to predict early events in a relapsed setting. Indeed, the duration of response to first-line therapy (POD24) was the only prognostic factor that was correlated to both PFS2 and SAR. Having excluded HT cases from our study population, we may suggest that poor outcomes associated with early progression after first-line therapy are likely independent of transformation.

A second observation was the strong correlation of outcomes after the first relapse with the duration of response to second-line therapy, analyzed through POD24r. Mirroring the definition of POD24, we empirically defined the 24-month cut-off to assess the prognostic impact of the duration of the second remission. We acknowledge that this choice might represent a possible limitation of our study. Waiting for larger and confirmatory studies, however, we believe our observation is supported by data and allows some additional considerations.

First, compared to available data concerning first-line settings, the risk of early relapse to second-line therapy is higher being reported in approximately half of the cases. Second, the risk of death associated with POD24r is very high, with a 19-fold higher risk of SAR compared to late relapses. Nevertheless, like POD24, not all POD24r patients had a bad outcome, with approximately two-thirds of patients alive at the 4-year timepoint. This last observation confirms the high heterogeneity of patients' outcomes also in the second-line setting and prompted us to analyze the correlations between POD24 and POD24r. As expected, we were able to show the strong correlation between POD24 and POD24r, with three out of four POD24r who were also POD24 and with a 49% probability of experiencing a short duration of second remission for POD24 patients. Importantly, no additional clinical or laboratory feature was predictive of POD24r risk.

Finally, one relevant observation from our study is that a potential transition from poor to good prognosis in R/P FL is possible and is likely the result of the adoption of effective salvage therapies. In our cohort, 44% of 48 POD24 cases achieved a PFS2 exceeding 24 months, indicating good efficacy of second-line therapies. Conversely, patients with POD24r and those who experienced both POD24 and POD24r faced a 21.8-fold and 29.2-fold higher risk of death, respectively. This finding underscores the distinctive prognostic value of POD24r on survival, establishing it as a robust predictor in the studied context. In particular, the observation of a good prognostic group among POD24 cases favorably compared with those reported by Muntanola et al., who retrospectively evidenced a favorable outcome for POD24 patients without HT and with a low-intermediate FLIPI at relapse.[14]

Given the retrospective nature of this study, our results require validation in larger cohorts. When confirmed, these observations might impact the approach to relapsed/refractory FL (R/R FL). First, they introduce the possibility that effective therapies can overcome the adverse prognostic features of patients with POD24. Furthermore, they imply that response duration should be considered for prognostic purposes only relative to the most recent line of therapy rather than as an absolute patient characteristic. Consequently, studies on FL therapy after first-line treatment should be cautious in universally identifying POD24 as a poor prognostic factor.

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AUTHOR CONTRIBUTIONS

Stefano Luminari, Alberto Bavieri, and Maria Elena Nizzoli ideated the study, collected data, analyzed data, and wrote the manuscript. Alessandra Tucci, Vittorio Ruggero Zilioli, Jacopo Olivieri, Benedetta Bianchi, Mansueto Giovanna Rosaria, Ombretta Annibali, Alessia Bari, Gloria Margiotta Casaluci, Michele Cimminiello, Nicola Di Renzo, Federica Cavallo, Vicenzo Pavone, Clara Mannarella, Annalisa Arcari, Maggi Alessandro, Antonella Anastasia, and Vittoria Tarantino contributed with cases and approved the manuscript. Antonino Neri, Massimo Gentile, and Fortunato Morabito collected cases, performed the statistical analysis, and wrote the manuscript. All co-authors approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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