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REVIEW

Early Relapse in First-Line Follicular Lymphoma: A Review of the Clinical Implications and Available Mitigation and Management Strategies

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ABSTRACT

Chemoimmunotherapy with rituximab (R-chemo) or obinutuzumab (G-chemo) is standard of care for patients with previously untreated symptomatic or high-tumor-burden follicular lymphoma. Median progression-free survival (PFS) with R-chemo plus R maintenance exceeds 10 years, and G-chemo plus G maintenance improves PFS relative to the corresponding R-containing regimen. Despite these positive results, a sizable proportion of patients continue to progress during or shortly after initial treatment. While no single definition of early relapse has been established, progression of disease within 24 months of initial treatment (POD24) is now widely accepted as a critical adverse prognostic factor. Multiple studies have shown increased mortality risk in patients with POD24 versus those without POD24. Unfortunately, tools for the assessment of POD24 risk are suboptimal, and it is not currently possible in clinical practice to identify individual patients who are at increased risk for early relapse. Treatment strategies for patients with POD24 are not well defined. G-chemo regimens appear to reduce the risk of POD24 relative to R-chemo regimens, although the impact on survival outcomes remains unclear. Beyond standard therapy, autologous stem cell transplant and emerging treatment modalities, such as bispecific antibodies and chimeric antigen receptor T-cells, may have a role in future management. Until standard treatments are defined, mitigating the risk of early relapse with effective up-front treatment remains the priority.

Keywords: Autologous stem cell transplant (ASCT); Bispecific antibodies; Chimeric antigen receptor (CAR)-T cells; Follicular lymphoma; Obinutuzumab; Progression of disease within 24 months of initial treatment (POD24); Rituximab

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Key Summary Points

Multiple studies have shown increased mortality risk in patients with follicular lymphoma (FL) who have progression of disease within 24 months of initial treatment (POD24) versus those who do not have POD24.

In clinical practice, it is not currently possible to identify individuals who are at increased risk for POD24. Improved tools for risk assessment are needed.

G-chemotherapy appears to reduce the risk of POD24 relative to R-chemotherapy in patients with previously untreated FL, but the impact on overall survival remains unclear.

Treatment strategies for the management of patients with POD24 are not well established. Well-designed studies are needed to determine the role of standard and emerging therapies.

In the absence of treatment standards, reducing the risk of POD24 with effective first-line therapies remains a priority.

INTRODUCTION

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL) [1, 2]. It accounts for approximately one-third of all NHL cases and 70% of indolent NHL cases. The median age at which FL is diagnosed is 65 years [1, 3]. Although often an indolent disease, FL has the potential to transform into a more aggressive form (e.g., diffuse large B-cell lymphoma [DLBCL]). Such transformation is a major contributor to early disease progression. In the PRIMA trial, 58% of the documented cases of histologic transformation (HT) occurred within the first year of follow-up after completion of induction treatment with chemoimmunotherapy [4], while other studies have also shown high incidence of transformation in the early stages of follow-up [5, 6].

Treatment strategies for FL vary considerably depending upon disease stage and risk stratification [2, 7, 8]. Watchful waiting or the use of single-agent monoclonal anti-CD20 antibody rituximab are often selected for patients with low tumor burden and no symptoms [7, 8]. For those with symptomatic disease or a high tumor burden, chemoimmunotherapy is recommended [7–9], as it has been shown in multiple studies to provide superior survival compared with chemotherapy only [10]. Rituximab maintenance strategies are recommended for patients with a response to initial chemoimmunotherapy and have been shown to improve progression-free survival (PFS) and time to next treatment (TTNT) [7, 11, 12]. The phase III GALLIUM trial demonstrated that the glyco-engineered type II anti-CD20 monoclonal antibody, obinutuzumab (GA101), plus chemotherapy (G-chemo) followed by obinutuzumab maintenance improves outcomes by significantly prolonging PFS and TTNT compared with the corresponding rituximab-based regimen in previously untreated FL patients [13, 14]. Consequently, G-chemo is now recognized as an alternative to rituximab plus chemotherapy (R-chemo) for first-line treatment of FL in patients [1, 8] for whom increasing the time before FL progression and/or next treatment is considered to be an important goal by the physician and patient.

Current rituximab- and obinutuzumab-based therapies have produced favorable outcomes, with 3-year PFS rates of up to 80% and median PFS of up to 10.5 years [11, 13, 15]. FL is, however, still considered to be incurable and some patients experience unfavorable outcomes [16], in particular those who relapse or progress early, for whom more effective first-line options are needed [13, 17, 18]. Multiple prognostic systems for identifying patients at risk of early relapse before treatment initiation have been developed, but additional research is needed to guide their real-world utility.

The aims of this review are to explore the definition and prognostic relevance of early relapse, to investigate methods for predicting which patients will relapse early, and to discuss

potential treatment strategies once relapse has occurred. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Defining Early Relapse

A consistent definition of early relapse is lacking, with differing time scales and endpoints considered in the literature. There are cross-study variances between the starting point considered by the authors, i.e., time to relapse from diagnosis [18–20] versus time from randomization or treatment initiation (Table 1) [21, 22]. In the National LymphoCare Study, Casulo et al. analyzed progression of disease (POD) rates at 1, 2 or 3 years post-diagnosis. They recommended evaluating POD at 2 years (POD24) for FL patients receiving rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) because data from previous studies repeatedly show that 20% of patients experience POD by this time, indicating that the peak risk of progression is within the 2 years following diagnosis [18]. Maurer et al. assessed the prognostic impact of event-free survival (EFS) at 12 and 24 months (EFS12 and EFS24) post-diagnosis in a cohort of 412 FL patients, by examining mortality rates in patients who achieved or did not achieve EFS12 or EFS24 [19]. The populations failing to achieve EFS12 or EFS24 (and in particular those who failed to achieve EFS12) showed significantly increased mortality compared with the age- and sex-matched general population. The authors advocated using EFS24 in patients receiving chemoimmunotherapy and EFS12 in those receiving non-aggressive therapy in order to assess prognosis. The European Society for Medical Oncology guidelines consider early relapse to occur within 12–24 months, although the starting point is not cited [7].

Moreover, differences in the definition of what constitutes a POD24 event makes cross-study comparisons difficult (Table 1). The EFS definition by Maurer et al. includes time to relapse or progression, unplanned retreatment of lymphoma after initial management, or death from any cause. The EFS definition used by Bachy et al. [20] is similar, including time to the same components as the Maurer et al. definition, or time to last contact. In contrast, the definition by Herold et al. incorporates just progression of disease or death from NHL. The proportion of patients identified as meeting the POD24 criteria differs between studies depending on the definition used (although study treatments may confound these differences).

While no single definition of early relapse is universally accepted, based on the above information, POD24 has become a widely adopted means of identifying patients with poor prognosis [23–26]. POD24 is a broad definition that encompasses a wide range of patients, including those with either low or high tumor burden, recurrence without any sign of transformed FL, and those with transformed FL. Of note, the studies that have evaluated the prognostic value of POD24 have done so with regard to patients treated with R-chemo. In the context of newer treatments, more specific definitions could be helpful for future refinement of risk stratification and treatment approaches.

Frequency of Early Relapse

Prior to the introduction of rituximab, approximately one- to two-thirds of FL patients experienced disease progression, relapse, or death within 2 years of starting first-line treatment [22, 27–30]. The addition of an anti-CD20 antibody to chemotherapy has been shown to reduce the incidence of POD24, with the incidence varying according to the chemotherapy backbone used (highest rate seen with cyclophosphamide, vincristine, and prednisone [CVP]), although caution is needed when comparing rates across trials, given the caveats mentioned above. A study of CHOP chemotherapy versus R-CHOP as first-line treatment for FL [22] showed that, after a median follow-up of 18 months, median time to treatment failure was significantly longer with R-CHOP compared with CHOP ($P < 0.001$). Treatment failure occurred within 24 months in ~ 37% of patients receiving CHOP, compared with ~ 19% of those receiving R-CHOP.

Table 1 Rates of progression of disease within 24 months (POD24) in studies of rituximab as first-line therapy for follicular lymphoma

Study	Treatment	Number of patients	POD24 definition	POD24 rate (percentage of patients)
Trials without anti-CD20 maintenance therapy				
Hiddemann et al. (GLSG'00)[22]	CHOP vs. R-CHOP followed by treatment intensification or IFN-α maintenance	428	Treatment failure (resistance to initial therapy, progressive disease, or death) within 24 months from the start of treatment	~ 37% vs. ~ 19%
Marcus et al. [27, 28]	CVP vs. R-CVP	321	Disease progression, relapse, or death within 24 months from study randomization	~ 65% vs. ~ 35%
Herold et al. [29]	MCP vs. R-MCP + IFN maintenance	358	PFS (progression of disease or death from NHL) within 24 months of randomization	~ 48% vs. ~ 15%
Salles et al. (GELA-GOELAMS FL2000) [30]	CHVP + IFN maintenance vs. R-CHVP + IFN maintenance	358	EFS (progression, relapse, start of new treatment, or death from any cause) within 24 months of randomization	33% vs. 21%
Federico et al. (FOLL05) [71]	R-CVP vs. R-CHOP vs. R-FM	504	Treatment failure (less than PR, change of therapy after at least cycle 1, progressive disease or relapse, or death) within 24 months of study entry	56% vs. 50% vs. 44%
Rummel et al. [72]	BR vs. R-CHOP	514	PFS (progression of disease, relapse after response, or death from any cause) within 24 months from first treatment	~ 22% vs. ~ 40%
Trials with anti-CD20 maintenance therapy				
Bachy et al. (PRIMA) [20]	R-chemotherapy (R-CHOP, R-CVP, R-FCM) followed by (in responders) R-maintenance or observation for 2 years	1135	Death from any cause, disease relapse or progression, unplanned retreatment of lymphoma after initial management, or the date of last contact within 24 months from diagnosis	~ 25% in the combined cohort

Table 1 continued

Study	Treatment	Number of patients	POD24 definition	POD24 rate (percentage of patients)
Fowler et al. (RELEVANCE) [32]	R-chemotherapy (R-CHOP, R-CVP, or R-bendamustine) followed by R-maintenance for 2 years vs. R-Len	517	100 minus 2-year PFS rate	13% (assessed by independent review committee) or 17% (investigator-assessed) R-chemotherapy 16% (assessed by independent review committee or investigator) R-LEN
Seymour et al. (GALLIUM) [25]	R/G-chemotherapy (R/G-CHOP, R/G-CVP, or R/G-bendamustine), followed (in responders) by R/G-maintenance for 2 years	601	Progressive disease or death due to progressive disease within 24 months of randomization to first-line treatment	16% R-chemotherapy 9% G-chemotherapy
Jurinovic et al. (GLSG'00 and BCCA) [33]	R-CHOP and IFN-α maintenance (GLSG) or R-CVP followed by R-maintenance (BCCA)	132 (GLSG) and 102 (BCCA)	Relapse or progression of FL within 24 months of starting 1st-line treatment	17% (GLSG) and 23% (BCCA)

BCCA British Columbia Cancer Agency, *BR* bendamustine and rituximab, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CHVP* cyclophosphamide, Adriamycin, etoposide, and prednisolone, *CVP* cyclophosphamide, vincristine, and prednisone, *EFS* event-free survival, *FCM* fludarabine, cyclophosphamide, and mitoxantrone, *FM* fludarabine and mitoxantrone, *G* obinutuzumab, *GLSG* German Low-Grade Lymphoma Study Group, *IFN* interferon, *Len* lenalidomide, *MCP* mitoxantrone, chlorambucil, and prednisolone, *NHL* non-Hodgkin lymphoma, *PFS* progression-free survival, *PR* partial response, *R* rituximab

A comparison of CVP with R-CVP showed that the CVP-treated patients progressed earlier, with median time to progression of 15 months versus 32 months, respectively [27]. Disease progression, relapse, or death occurred within 24 months in 65% of CVP-treated patients, compared with 35% of those treated with R-CVP. Analyses after R-bendamustine (R-benda)-based induction also suggest low risk of POD24 events (12–18%) [21, 31]. With a demonstrated favorable adverse effect profile and suggestion of superior disease control, bendamustine-based therapy has become a commonly used induction strategy for FL patients with symptomatic advanced-stage disease. In GALLIUM, the rate of POD24 events appeared to be lower in patients who received G-benda (7.0%) than in those who received G-CHOP (11.8%), while the POD24 rate appeared to be similar in patients who received R-benda (15.2%) or R-CHOP (15.8%) [25].

Administering rituximab maintenance after induction treatment with R-chemo may further reduce the risk of early progression, although with maintenance therapy, the emphasis is usually on longer-term outcomes. Reported incidence rates for POD24 studies employing rituximab maintenance after R-chemo-based induction range between 13% and 25% [20, 25, 32, 33].

Obinutuzumab has been shown to display higher antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated phagocytosis, and direct cytotoxicity than rituximab [34, 35]. In the primary analysis of the GALLIUM trial, the estimated 3-year PFS was 80% with G-chemo and 73% with R-chemo (hazard ratio [HR] for progression, relapse, or death, 0.66; $P = 0.001$) [13]. The recent exploratory analysis presented in Table 1 reported that G-chemo and maintenance reduced the risk of POD24 compared with R-chemo and maintenance (cumulative incidence of POD24 events: 10% vs. 17%, respectively, average HR-based reduction in risk: 46% [95% CI: 25.0–61.1], $P = 0.0003$ [25]. At a median follow-up of 41 months, HT to more aggressive lymphoma occurred in 35 patients overall (G-chemo 2.2% of patients; R-chemo 3.7%) and in 30 patients who experienced POD24 (G-chemo 19.3%; R-chemo 19.4%). It should be noted that, although G-chemo was associated with improved PFS and a reduced risk of POD24 relative to R-chemo in GALLIUM, a corresponding improvement in overall survival is yet to be observed.

Incidence of early progression has also been evaluated in patients treated with other novel agents. The possibility of a chemotherapy-free treatment regimen in first-line FL was investigated in the RELEVANCE trial, by comparing R-lenalidomide (R^2) with R-chemo [32]. There was no significant between-group difference in the proportion of patients who had progressed or died at 2 years (R^2, 16% vs. R-chemo, 13% [independent review committee-assessed]; 16% vs. 17%, respectively [investigator-assessed]), suggesting that POD24 might be similar for the two treatments. Similarly, in the GALEN trial, at 2 years, 15% of FL patients who received first-line treatment with G-lenalidomide had progressed or died. [36]

Prognosis in Patients with Early Relapse

There is strong evidence of reduced survival among patients who experience POD24, compared with those not progressing within 24 months [18, 26]. In an analysis from the observational National LymphoCare Study of FL patients who received R-CHOP as first-line treatment, 5-year OS rates in those with POD24 versus those without were 50% and 90%, respectively (Fig. 1) [18]. In the independent validation cohort of FL patients who also received R-CHOP as first-line treatment, 5-year OS rates were 34% and 94%, respectively. Similarly, a study by Jurinovic et al. reported 5-year overall survival (OS) rates of 41% versus 91% in patients with and without POD24, respectively, in patients treated with R-CHOP followed by interferon-α maintenance, and 26% versus 86%, respectively, in patients treated with R-CVP followed by rituximab maintenance [33]. Survival in FL patients receiving chemoimmunotherapy as first-line treatment was also assessed in a study designed principally to evaluate the PRIMA Prognostic Index (PRIMA-PI) [37]. The likelihood of survival at 7 years was 51.9% in patients with POD24 and 91.9% in those without ($P < 0.0001$). An exploratory landmark analysis of the GALLIUM trial was also performed to compare survival in patients with versus without a POD24 event [25]. Two-year OS rates from the 24-months landmark (i.e., in patients still alive at 24 months) in the two groups were 82.4% and 98.2%, respectively (age-adjusted HR, 12.2 [95% confidence interval 5.6–26.5]; Fig. 2). Two-year OS rates were lower in patients who had had a progression of disease event within 6, 12, or 18 months of treatment initiation (Fig. 2). At a follow-up of 22.6 months, post-progression survival was similar across treatment arms for patients with POD24 (19/57 [33%] G-chemo, 37/98 [38%] R-chemo). The proportion of POD24 patients surviving at 2 years after progression was 66% (95% confidence interval 58.3–73.9). Further studies in FL patients receiving chemotherapy

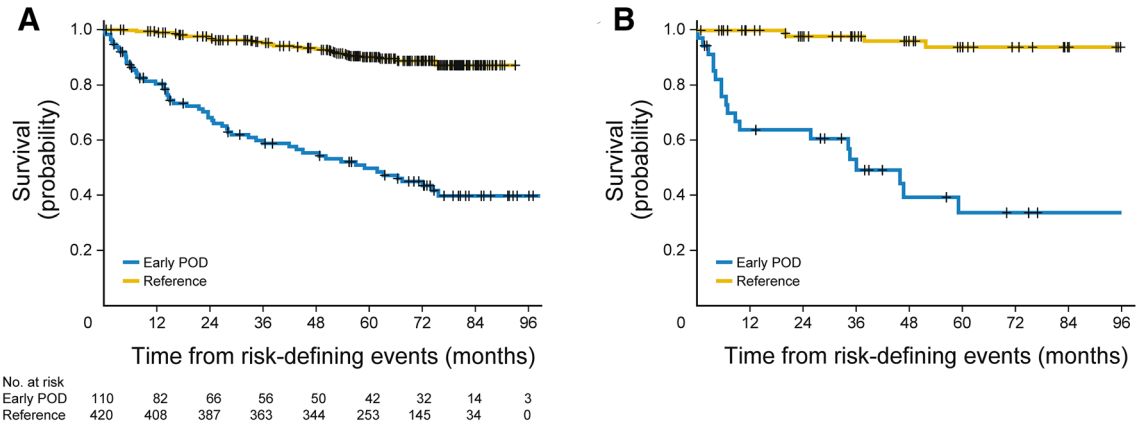


Fig. 1 Overall survival in **A** the National Lymphocare Study and **B** the independent validation cohort: comparison of FL patients with POD24 ("early POD") versus patients without POD24 ("reference") [18]. Reproduced with permission. Copyright © 2015, Wolters Kluwer Health. *POD* progression of disease

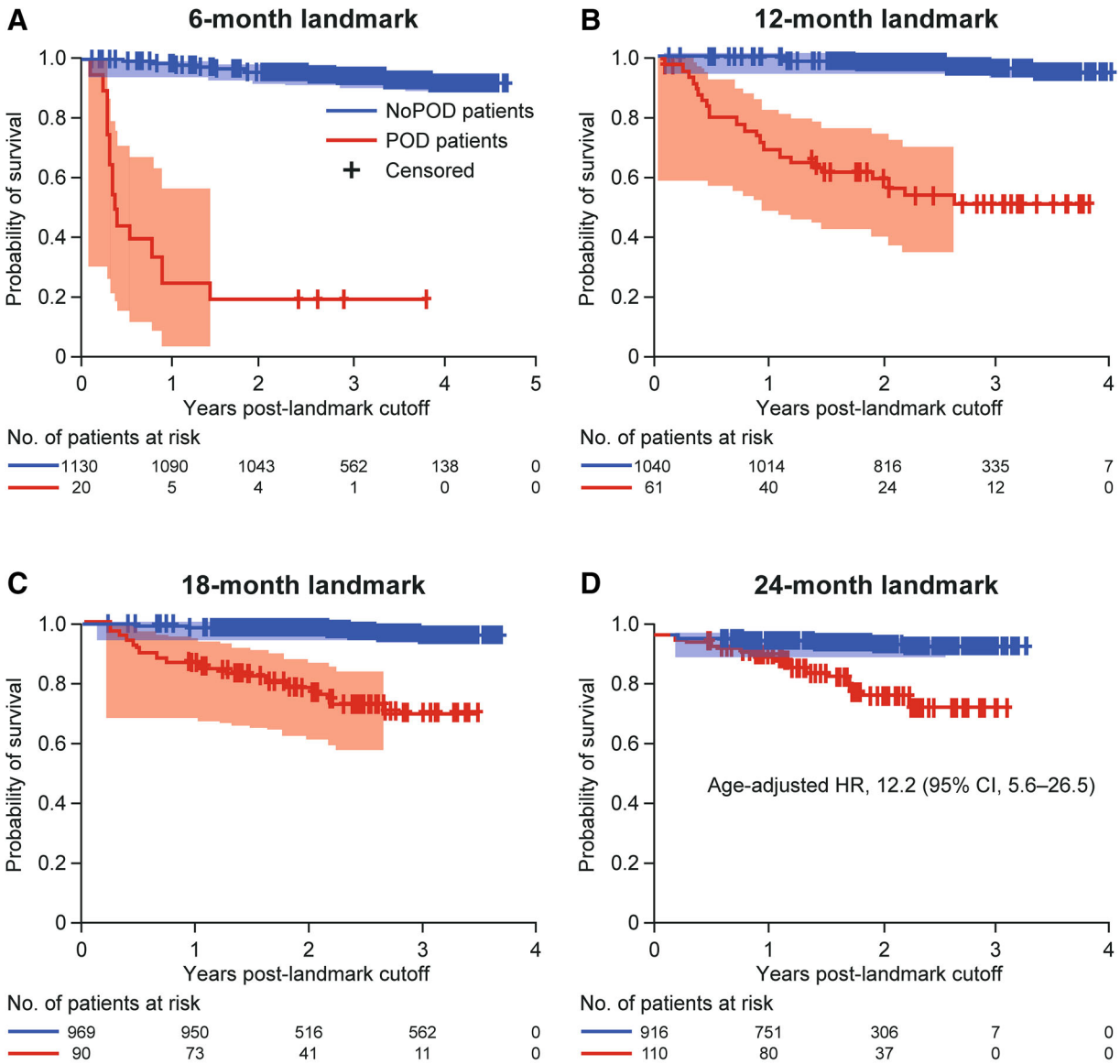
or chemoimmunotherapy, published only in brief at the time of writing, have also reported significantly reduced OS in patients with versus without POD24 [24, 38, 39].

The prognostic value of POD24 for patients initially treated with chemotherapy-free regimens has also been evaluated. In a combined retrospective analysis of patients treated with non-chemotherapy rituximab-based doublets, Lansigan et al. found that patients with POD24 had a lower 2-year survival rate compared with those without POD24 (80% vs. 99%, respectively). Corresponding 5-year survival rates were 74% and 90%, respectively [40]. Furthermore, data presented by Moccia et al. showed that POD24 was associated with significantly reduced OS in a combined analysis of patients receiving R^2 or rituximab monotherapy [41]. Five-year OS was 69% for patients with POD24 and 92% for those without (HR 3.12 [95% confidence interval 1.73–5.65]). However, interpretation of these studies is limited by the retrospective nature of the analyses of pooled patients, and in the Lansigan study, antibodies not approved for the treatment of FL were included as partners with rituximab.

Variation in prognosis between patients with versus without early relapse when parameters other than POD24 are used is also of interest. Data from a cohort of FL patients receiving a range of first-line treatments show large differences in standardized mortality rates (SMRs) between patients who were event-free and those who had experienced an event at 12 months (1.75 vs. 10.27) or 24 months (1.30 vs. 8.42), respectively [42]. The data from this study suggest that overall mortality rates in FL patients without early relapse are close to those of age- and sex-matched controls from the general population. Indeed, in another study of patients receiving a range of different first-line treatments, those achieving EFS12 showed a trend towards lower mortality than age- and sex-matched controls, with an SMR of 0.73 (95% confidence interval 0.56–0.94) [19]. There is also evidence that the earlier patients relapse, the worse their prognosis will be [18, 25, 42]. In the GALLIUM trial, the number of deaths per 100 patient-years was 3.8 if progression occurred at 18 to 24 months, and this increased to 81.0 with progression at 0–6 months [25].

What Does POD24 Mean?

These data raise the question of the significance of early progression, and in particular the presence of HT at the time of treatment initiation. A significant proportion of patients who relapse early exhibit HT. In the GALLIUM trial, 20.3% of POD24 patients showed transformation within 24 months, compared with 3.3% in the



	POD		noPOD	
Landmark	OS (%) at 2 years post-landmark	95% CI	OS (%) at 2 years post-landmark	95% CI
6 months	20	2.5–37.5	95.8	94.6–97.0
12 months	58.4	45.5–71.3	97.6	96.7–98.6
18 months	76.5	67.0–86.0	97.8	97.0–98.9
24 months	82.4	74.2–91.34	98.2	97.1–99.2

◀**Fig. 2** Landmark analysis of OS in patients with and without a progressive disease event before the 6-, 12-, 18-, and 24-month landmarks in GALLIUM. The shaded sections are the 95% Hall-Wellner confidence bands for the period during which patients died. Two-year OS estimates are presented in the table [25]. Reproduced with permission. Copyright © 2020, Ferrata Storti Foundation. *CI* confidence interval, *HR* hazard ratio, *POD* progression of disease, *OS* overall survival

overall study population [43]. However, these data were not based on systematic biopsy of all study participants; of 315 patients who had progressed at the time of the analysis, only 46 (14.6%) were biopsied at first relapse due to suspicion of transformation. It is possible that a systematic approach would show that a higher percentage of patients had transformation. In addition, in the case of FL relapse, the recommendations are to biopsy the nodal site with the highest standardized uptake value (SUV; SUV_{max} correlates with a higher probability of HT), which is not always possible in clinical practice. Thus, both the lack of biopsy in a large percentage of relapsed patients and the potential for the biopsy not to have been performed in the node with the highest probability of HT likely contribute to underestimated HT levels. In an analysis with median follow-up of 73 months from the PRIMA cohort, 42% (194/463) of patients who experienced progression were biopsied, of whom 40 (20.6%) had HT. Of note, more than 50% of cases of transformation occurred during the first year of follow-up [4]. HT is associated with very poor prognosis; in the GALLIUM trial analysis, with a median follow-up of 57.3 months, of the POD24 patients, 51.6% of those with transformation and 27.0% of those with relapsed FL died within 2 years of the POD event [43]. Patients with HT in the PRIMA analysis had shorter OS from recurrence than patients relapsing with FL histology, 3.8 versus 6.4 years, respectively ($P < 0.001$) [4]. In a study by Maurer et al., which included two patient cohorts, POD24 patients with transformation showed significantly reduced 5-year OS rates compared with POD24 patients with progression of FL (cohort 1: 27% vs. 54%, respectively, HR 0.36 [95% confidence interval 0.19–0.70]; cohort 2: 31% vs. 61%, respectively, HR 0.45 [95% confidence interval 0.22–0.89]) [44]. Thus, patients who experience POD24 with HT have a worse prognosis than those with POD24 due to FL progression.

Therefore, there is considerable evidence for POD24 as a prognostic marker, and the data indicate that more aggressive treatments are needed in these patients at relapse; however, (i) there remains difficulty in identifying at diagnosis those patients who will experience POD24, and (ii) even if these patients can be determined up front, the first-line treatment options that would reduce the likelihood or prevent the patient experiencing a POD24 event are unknown.

Predicting Which Patients Will Relapse Early

The risk of experiencing POD24 is difficult to determine and could be related to multiple disease- and patient-related factors. A number of prognostic indices exist, based on clinical or clinical and genetic factors, which have been evaluated for utility in predicting POD24.

The Follicular Lymphoma International Prognostic Index (FLIPI) is based on patients' age, disease stage, number of affected lymph node sites, and levels of lactate dehydrogenase and hemoglobin, and was developed before the introduction of rituximab, but has been validated in patients receiving chemoimmunotherapy [20, 45]. FLIPI has demonstrated sensitivity of 60–78% and specificity of 56–62% for predicting POD24 (Table 2).

The FLIPI2 index is based on patients' age, longest diameter of the largest involved lymph node, bone marrow involvement, and levels of hemoglobin and β2-microglobulin, and was derived using prospectively collected data in the R-chemo era [46]. The FLIPI2 index has shown similar sensitivity (53%) and greater specificity (76%) relative to FLIPI for prediction of POD24 [47].

In 2018, Bachy et al. reported the development of the PRIMA-PI, a simplified prognostic score based on two factors (β-2-microglobulin level [> 3 mg/L vs. ≤ 3 mg/L] and bone marrow

Table 2 Performance of three indices in the prediction of POD24 among FL patients

Patient cohort	POD24-PI		FLIPI		m7-FLIPI		PRIMA-PI		FLEX	
%	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
GLSG Jurinovic et al. [33]	78	67	78	56	61	79	–	–	–	-
BCCA Jurinovic et al. [33]	61	73	70	58	43	86	–	–	–	-
PRIMA Huet et al. [47]	54	72	60	62	46	77	–	–	–	-
GALLIUM Mir et al. [48]	–	–	53[a]	59[a]	–	–	69	47	60	68

BCCA British Columbia Cancer Agency, *FL* follicular lymphoma, *FLIPI* Follicular Lymphoma International Prognostic Index, *GLSG* German Low-Grade Lymphoma Study Group, *PI* Prognostic Index, *POD24* progression of disease within 24 months

[a] FLIPI and FLIPI-2

involvement [yes vs. no]), and compared its use with FLIPI in predicting EFS24 in the PRIMA study population [20]. In this study, each index was used to define three patient groups (low-, intermediate-, and high-risk). Percentages of patients in the three respective groups with EFS24 were 14%, 21%, and 38% with PRIMA-PI, compared with 16%, 21%, and 31% with FLIPI. Therefore, although both indices were able to distinguish between risk levels, the results indicate that neither would predict which individual patients would experience EFS24 with high accuracy.

The Follicular Lymphoma Evaluation Index (FLEX), a model based on nine routinely assessed clinical variables, was recently reported by Mir et al. [48]. FLEX was developed using data from the phase III GALLIUM trial. In first-line FL patients from GALLIUM, FLEX showed higher sensitivity (60% vs. 53%, respectively) and specificity (68% vs. 59%, respectively) for predicting POD24 than FLIPI and FLIPI2.

The addition of genetic markers to clinical factors has been explored as a potential means to improve the predictive ability of the prognostic indices. The m7-FLIPI, which includes the mutation status of seven genes along with standard FLIPI criteria, and Eastern Cooperative Oncology Group performance status (ECOG PS) was developed for improved identification of high-risk patients [49]. A study by Jurinovic et al. using two independent patient cohorts demonstrated lower sensitivity (43–61% vs. 70–78%) but greater specificity (79–86% vs. 56–58%) of m7-FLIPI compared with FLIPI, respectively, for predicting POD24 [33]. The POD24 prognostic index (POD24-PI) [33] is based on high-risk gene mutations, clinical risk factors (FLIPI $>$ 2; i.e., high-risk FLIPI), and poor performance status (ECOG PS $>$ 1). In the study by Jurinovic et al., POD24-PI exhibited higher sensitivity than m7-FLIPI and higher specificity than FLIPI (Table 2) [33]. Based on its high specificity, the authors concluded that m7-FLIPI is the most promising index for POD24 prediction. A more recent study used a similar methodology to compare these indices in patients participating in the PRIMA study [47]. The outcomes were similar to those reported by Jurinovic et al. (Table 2), and the authors highlighted the potential applicability of m7-FLIPI and POD24-PI.

Using solely genetic factors to assign risk, Huet et al. investigated the prediction of POD24 using a 23-gene expression signature to stratify patients into low- and high-risk groups [50]. Using this method, POD24 was predicted with sensitivity of 43% and specificity of 79% (POD24 rates in the low- and high-risk groups were 19% and 38%, respectively). These values appear to compare well with other indices, and comparative studies would be of interest.

Immunobiology represents a possible alternative means of predicting the risk of POD24. Tobin et al. found that tumors with low levels of PD-L2 expression had reduced infiltration with macrophages and T-cell clones [23], and patients with tumors with reduced immune infiltration were more likely to have a POD24 event. The specificity of this method was high (83.7%); however, sensitivity was not (45.7%).

The above results indicate that we do not yet have a tool that provides sufficient sensitivity and specificity to accurately predict whether a given patient in clinical practice will experience POD24. Some of the indices described above (e.g., PRIMA-PI and FLEX) were designed to simplify the assessment process, for example by using readily available clinical information. The m7-FLIPI and the 23-gene expression signature require analysis of gene mutations that may not always be assessed in clinical practice, although some consideration of genetic characteristics may be required to enable accurate risk prediction. Moreover, the prognostic ability of the m7-FLIPI has been shown to be dependent upon the chemotherapy utilized [51, 52]. Importantly, the ease with which predictive tools can be used in clinical practice, as well as their prognostic accuracy, will affect their overall implementation rates.

Mitigation Strategies

The current limitations in predicting which patients will experience POD24 confound upfront tailoring of treatment according to POD24 risk. These limitations are compounded by the lack of a single, universally agreed definition for

POD24 and by the need to consider optimal maintenance as well as induction therapy.

It is important to develop methods for predicting the likelihood of HT before treatment of FL is initiated. A recent retrospective analysis indicated that the impact of POD24 on prognosis could be reduced by assessing patients with positron emission tomography (PET) imaging before initiating treatment [53]. This may be attributable to improved detection of disease transformation at baseline compared with computed tomography imaging. Thus, PET-based imaging may potentially enable patients who would have previously been included within the FL population (and probably shown later to have HT) to be diagnosed and perhaps treated differently from the outset. However, it should be noted that an exploratory analysis from GALLIUM found that baseline PET-based SUV_{max} could not be used to predict patients who would undergo HT [54].

In the meantime, administration of the most effective available regimen (antibody and chemotherapy) could help restrict the number of patients relapsing early. Current data show that obinutuzumab-based chemoimmunotherapy can significantly reduce the risk of early progression. In the absence of reliable methods for baseline identification of POD24 patients, such data may justify routine, first-line use of obinutuzumab-based chemoimmunotherapy treatment regimens in FL. Further clinical trials and large-scale real-world data evaluations including obinutuzumab-based therapies are needed to optimize our strategies.

In addition, rigorous monitoring of treatment response is critical to further understand the efficacy of potential POD24 mitigation strategies. An analysis of GALLIUM data has shown that patients with a complete metabolic response (CMR) on PET imaging after induction therapy have longer PFS (HR 0.4 [95% confidence interval 0.3–0.6]; $P < 0.0001$) and OS (HR 0.2 [95% confidence interval, 0.1–0.5]; $P < 0.0001$) than patients who have a non-CMR [55]. It may be that patients who do not achieve CMR on PET after induction therapy should be biopsied to identify transformation and therefore risk of early relapse.

Treatment of Patients Following Early Relapse

Several treatment options may be able to mitigate the risk incurred with POD24. These include aggressive measures such as autologous stem cell transplantation (ASCT) or novel therapies such as obinutuzumab, PI3K inhibitors, and lenalidomide. Current treatment guidelines include recommendations for treating relapsed disease [2, 7, 8]. However, these recommendations are not specific to a particular definition of relapse, and POD24 patients may be considered as a distinct subgroup.

Few studies of chemoimmunotherapy have been performed specifically in patients with early relapse. Van Oers et al. demonstrated that PFS can be extended with rituximab maintenance in patients with relapsed/resistant disease after R-CHOP induction: median PFS was 51.5 months with rituximab maintenance therapy, versus 14.9 months with observation ($P < 0.001$) [56]. The eligibility criteria for the study by van Oers et al. included "relapse after or resistance to a maximum of two non-anthracycline-containing systemic chemotherapy regimens," meaning that patients not meeting POD24 criteria were included (in half of the patients, time from initial diagnosis of FL to study entry exceeded 2 years).

Reducing the risk of POD24 may not necessarily translate into long-term benefit. In the PRIMA study, more patients in the rituximab maintenance arm avoided POD24; however, they were less likely to respond well to next-line therapy [11]. The complete response (CR) rate (confirmed or unconfirmed) among the subgroup experiencing POD24 was worse in the rituximab maintenance arm compared with the observation arm (39.3% vs. 56.3%; $P = 0.029$). This suggests an increased likelihood of aggressive, less responsive disease among patients who relapse while on maintenance therapy; however, more data are needed to draw definite conclusions.

Aggressive cellular strategies such as ASCT could be an option for fit patients who experience POD24. One study of ASCT was performed in non-transformed FL patients; individuals with large-cell features and previous treatment

with rituximab were eligible for inclusion [57]. After transplantation, median PFS was 9.7 years and median OS was 21.3 years. Lack of change in PFS after 16 years in this study suggests the possibility of cure in patients not progressing before this time point. The same investigators subsequently studied ASCT as consolidation treatment in non-transformed FL patients showing second complete or partial response to rituximab-based therapy, following failure of first-line R-chemo within 2 years [58]. Five-year OS post-ASCT was 81% in this group.

The National LymphoCare Study included assessment of ASCT in FL patients experiencing early treatment failure (failure to achieve at least a partial response to up-front therapy, or POD24), performed within 1 year of first-line treatment failure; 5-year OS in patients undergoing ASCT was 73%, significantly higher than the 60% rate in patients not undergoing ASCT ($P = 0.05$) [59]. Smith et al. compared different methods of stem cell transplantation in patients experiencing relapse or progression within 2 years of first-line R-chemo [60]. There was no significant difference in the 5-year OS rate between patients undergoing ASCT or allogeneic transplantation with a sibling donor (70% and 73%, respectively). However, both of these groups showed superiority versus patients undergoing allogeneic transplantation with an unrelated donor, in whom the 5-year OS rate was 49% ($P < 0.001$ for both comparisons).

There is some evidence that patients with HT may be more likely to benefit from ASCT. In the PRIMA study, patients with transformed disease who received ASCT after initial salvage therapy showed improved OS compared with those who did not receive ASCT [4]. In contrast, ASCT had no apparent effect on OS among patients relapsing with FL. These results are not from a POD24 population, but remain relevant because HT is a notable contributor to POD24 rate. In summary, current evidence indicates that ASCT may be beneficial to patients experiencing POD24, most notably those with evidence of HT.

Immunomodulatory therapy with R^2 was investigated in two recent studies of patients with relapsed or refractory FL. The first of these studies showed significantly improved PFS with R^2 versus rituximab alone (median values of 39.4 months and 14.1 months, respectively) [61]. Further analysis showed that this effect was similar in patients with or without POD24 [62]. In the second study, which is ongoing, preliminary data show an overall response rate (ORR) of 73% and a CR rate of 45% with R^2 induction therapy [63]. Acceptable tolerability was reported in both studies. Treatment with G-lenalidomide has also been assessed in relapsed or refractory FL (G-lenalidomide given as induction for 24 weeks then as maintenance for 1 year, followed by a year of maintenance with obinutuzumab monotherapy) [36]. A response at the end of induction was observed in 79% of patients, and the PFS rate at 2 years was 65%. A post hoc analysis showed similar results (overall response 75% and 2-year PFS 63%, respectively) in patients with POD24. Of note, however, is that these studies excluded patients with evidence of HT, who would likely have a poor prognosis compared to patients without evidence of large-cell transformation.

PI3K inhibitors represent another possible option for treating POD24 patients. In 2014, idelalisib became the first drug in this class to be approved for treatment of FL and it has since been joined by copanlisib and duvelisib. A post hoc analysis of a single-arm study showed that in FL patients previously treated with first-line chemoimmunotherapy who had relapsed within 24 months, idelalisib monotherapy (median duration 8.2 months) resulted in a median PFS of 11.1 months [64]. In comparison, median PFS in the whole study population (i.e., patients who had not had a response to rituximab and an alkylating agent or had had a relapse within 6 months after receipt of those therapies) was 11.0 months [65]. Duvelisib was studied as monotherapy in patients with indolent NHL refractory to rituximab and either chemotherapy or radiotherapy [66]. Median values for PFS and OS were 9.5 months and 28.9 months, respectively, with an ORR of 47%. In the subgroup of patients with FL who experienced POD24 after first-line R-CHOP, median PFS was lower, at 8.2 months, with an ORR of 33%. In a study of copanlisib in patients with relapsed or refractory indolent NHL after at least two prior lines of treatment, a median PFS of

11.3 months and an ORR of 60% were reported for patients with POD24 [67]. Corresponding results were similar in patients with disease progression at 24 months or later (median PFS, 10.8 months and ORR, 59%).

Studies of alternative treatment approaches are currently in progress. For example, study S1608 (NCT03269669) is comparing response rates following G-umbralisib, G-lenalidomide, or G-chemo in FL patients relapsing within 2 years after first-line treatment with chemotherapy and anti-CD20 therapy [68]. In another study (NCT03105336), chimeric antigen receptor T-cell therapy is being assessed in indolent NHL patients with disease progression after at least two prior lines of treatment with chemoimmunotherapy [68]. An interim analysis with median follow-up of 11.5 months has shown an ORR of 94% in 87 patients [69]. Of note, 66% of patients included had experienced POD24 after their initial therapy. Recent data from a phase I dose-escalation trial (NCT02500407) of the CD20/CD3 bispecific antibody mosunetuzumab in 62 patients with relapsed or refractory FL (30 with POD24) demonstrated encouraging efficacy in both the overall patient population (ORR 68%; CR 50%) and patients with POD24 (ORR 73%; CR 53%) [70].

In summary, the optimal strategy for treating POD24 patients post-progression is yet to be defined. That being said, the above data show that aggressive modalities such as ASCT or novel therapies may lead to outcomes similar to those of patients who do not experience POD24. Further studies are needed to increase our understanding of the type, dose, and duration of treatment most likely to benefit patients experiencing POD24.

CONCLUSIONS

Despite substantial improvements in FL treatment over recent years, there remains a proportion of patients who relapse early and have poor prognosis. Optimal criteria for defining early relapse (assessment parameters as well as the time point) are not formally established, although POD24 is increasingly being used to assess early relapse in clinical trials. While no causal link has been established that shows that reducing POD24 decreases subsequent mortality, multiple studies have shown reduced survival in patients with versus without POD24. To enable personalized treatment, new tools are needed to identify whether a given patient is likely to experience POD24. Clinical trials are also needed to determine the optimal strategy for minimizing the occurrence of POD24 while improving these patients' prognosis, as well as how best to treat patients who experience early progression. In the meantime, the most effective first-line treatment regimens should continue to be utilized routinely in FL.

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