ARTICLE OPEN

Check for updates

Validation of POD24 as a robust early clinical indicator of poor survival in mantle cell lymphoma from 1280 patients on clinical trials, a LYSA study

Clémentine Sarkozy[1], Loïc Chartier[2], Vincent Ribrag[3], Remy Gressin[4], Christian H. Geisler[5], Hanneke C. Kluin-Nelemans[6], Catherine Thieblemont[7,8], Franck Morschhauser[9], François Lemonnier[10], Violaine Safar[11], Benoît Tessoulin[12], Lucie Oberic[13], Ghandi Damaj[14], Hervé Ghesquières[11], Krimo Bouabdallah[15], René Olivier Casasnovas[16], Roch Houot[17], Wolfram Klapper[18], Barbara Burroni[19], Christiane Pott[20], Marie-Hélène Delfau-Larue[21], Elizabeth Macintyre[22], Mary Callanan[23], Mats Jerkeman[24], Michael Unterhalt[25], Eva Hoster[26], Martin Dreyling[25], Steven Le Gouill[1], Olivier Hermine[27,28] and Morgane Cheminant[27,28]✉

In mantle cell lymphoma, early progression of disease has been associated with short overall survival. The impact of clinical, pathological, and treatment strategies on the risk of early relapse has not been assessed in a large cohort of patients. We performed a pooled analysis of patients recruited in France from six randomized first-line MCL trials. Among 1386 treated MCL patients, 1280 were evaluable for POD24 status: 299 (23.4%) with a POD24 event and 981 (76.6%) without. Patients with a POD24 event had a median OS of 9.3 months (95% CI 8.4–11.8) versus not reached (95% CI 97.8–NR) for those without POD24 events. The median post-relapse OS of patients with a late relapse was also significantly longer at 49.4 months (HR = 0.39; 95% CI 0.31–0.48; $P < 0.001$) as compared to POD24 patients. Baseline variables (age, performance status, B symptoms, LDH/ULN, leukocytes, blastoid variant, and Ki-67 > 30%) were significantly associated with the risk of POD24, independent of ASCT. Among responding patients at end-of-induction ($n = 1105$) who had received ASCT, anti-CD20 maintenance was associated with a decreased risk of POD24 (OR = 0.37; 95% CI 0.1–1.0). Using this large data set of patients in clinical trials, we confirm that POD24 status is strongly associated with subsequent OS in MCL. Rituximab maintenance provided significant protection against the risk of POD24, independent of ASCT. Progression within 2 years should be considered as a primary endpoint in future studies.

HIGHLIGHTS

- Progression within 2 years (POD24) is strongly associated with subsequent overall survival in Mantle Cell Lymphoma.
- Progression within 2 years should be considered as a primary endpoint in future studies.
- Rituximab maintenance was protected against the risk of POD24, independent of ASCT.

Blood Cancer Journal (2025)15:78 ; https://doi.org/10.1038/s41408-025-01241-9

[1]Hematology Departement, Institut Curie, Saint Cloud, Université de Versailles Saint-Quentin (UVSQ), Versailles, France. [2]Statistiques, Lymphoma Academic Research Organisation (LYSA), Piérre-Benite, France. [3]Haematology Department, Institut Gustave Roussy, Villejuif, France. [4]Haematology Department, Univ. Grenoble Alpes. University Hospital, Grenoble France & Institute For Advanced Biosciences (INSERM U1209), Grenoble, France. [5]Haematology Department, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [6]Haematology Department, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [7]Université Paris Cité, Inserm U1153, Paris, France. [8]Hemato-oncology Department, Hôpital Saint Louis, Assistance Publique – Hôpitaux de Paris, Paris, France. [9]Univ. Lille, CHU Lille, ULR 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France. [10]Haematology Department, Groupe Hospitalier Mondor, Assistance Publique Hôpitaux de Paris, Paris, France. [11]Haematology Department, Centre hospitalier Lyon Sud - 145 Chemin du Grand Revoyet, Pierre Bénite, France. [12]Haematology Department, Nantes University Hospital, Nantes, France. [13]Haematology Department, Institut universitaire du cancer Toulouse- Oncopole, Toulouse, France. [14]Haematology Department, Normandie University, Hematology Institute, Caen, France. [15]Haematology Department, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France. [16]Haematology Department, Centre Hospitalier Universitaire Dijon, INSERM UMR1231, Dijon, France. [17]Department of Hematology, University Hospital of Rennes, UMR U1236, INSERM, University of Rennes, French Blood Establishment, Rennes, France. [18]Institut für Pathologie, Sektion Hämatopathologie und Lymphknotenregister, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Kiel, Germany. [19]Department of Pathology, Cochin University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [20]University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Kiel, Germany. [21]Biological Haematology and Immunology Department, Groupe Hospitalier Mondor, Assistance Publique Hôpitaux de Paris, INSERM U955, Paris, France. [22]Biological Haematology Department, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [23]University of Burgundy-INSERM 1231-CHU Dijon, DIJON, France. [24]Department of Oncology, Institute of Clinical Sciences, Lund University and Skane University Hospital SE22185, Lund, Sweden. [25]Department of Medicine III, LMU University Hospital, Munich, Germany. [26]Institute for Medical Information Processing, Biometry, and Epidemiology, LMU Munich, Munich, Germany. [27]Haematology Department, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [28]Université Paris Cité, Institut Imagine, Laboratory of Hematological Disorders, INSERM UMR1163, Paris, France.
✉email: morgane.cheminant@aphp.fr

Received: 4 October 2024 Revised: 23 January 2025 Accepted: 20 February 2025
Published online: 24 April 2025

INTRODUCTION

The prognosis of patients with mantle cell lymphoma (MCL) has largely improved in recent decades. Indeed, the median survival rate reaches 9.8 years in elderly patients who respond to induction and receive rituximab maintenance [1, 2] and more than 10 years in younger patients who receive high-dose cytarabine followed by intensification and autologous stem cell transplantation (ASCT) [3–7]. However, despite these long-term responses, MCL is characterized by a heterogeneous clinical course with 20% of the patients presenting rapid progression or early relapse, including 5–10% with primary chemoresistance [8, 9], resulting in an OS of less than a year from the time of relapse.

For indolent lymphoma, it is now well established that progression or death within 24 months of treatment initiation, so-called POD24, is a robust indicator of poor survival, suitable as a primary endpoint in clinical trials [10–13]. In MCL, an EBMT registry analysis showed that relapse within 12 months after ASCT was associated with worse survival [14]. More recently, retrospective cohort studies identified POD24 as associated with short OS in MCL patients [4, 15, 16]. However, the predictive value of POD24 for OS prediction, independently from other clinical factors, therapeutic strategies, and in the rituximab maintenance era, still needed to be assessed, using data from patients included in trials. The Mantle Cell International Prognostic Index (MIPI) is a well-validated tool for prognostic stratification at diagnosis [17]. The MIPI, combined with Ki-67 score, allows the identification of high-risk patients with a 5-years overall survival (OS) of 17% in both younger and elderly populations [18, 19].

Given the improvement in long-term outcome for first-line MCL patients, robust prognostic markers for OS developed from large datasets of patients treated in the rituximab maintenance era are needed to define an early endpoint for future clinical trials aiming at the development of risk stratification strategies. The aim of our study was (1) to define the best time-dependent cutoff value for OS prediction and the potential of POD24 as a solid prognostic tool in a large cohort of patients included in first-line MCL clinical trials; (2) to investigate whether clinical factors at diagnosis could predict the risk of POD24 and (3) whether treatment strategies mitigate this risk.

PATIENTS AND METHODS

We analyzed individual patient data from previously untreated MCL patients enrolled in six multicenter trials conducted in the rituximab era and recruited in France (EU-MCL younger [7], LyMA [6], LyMA101 [20], EU-MCL elderly [1], RiBVD [21], and MCL-R2 [22] trials, see Supplementary data for additional information, Supplementary Tables 1 and 2). The studies were conducted in accordance with the Declaration of Helsinki. Overall survival (OS) is defined as time from trial registration (inclusion or randomization) to death from any cause. Cumulative progression/relapse incidence was computed with the Kaplan–Meier method. At first, to define the best time-dependent cutoff value for OS prediction, we modeled the relationship between time to progression of lymphoma (TTP) and risk of death from progression/relapse using a natural cubic spline transformation in a Cox proportional hazards model in patients with progression/relapse. POD24 is defined as progression/relapse or lymphoma-related death within 24 months from trial registration. Patients censored or with non-lymphoma-related death before 24 months were excluded from this analysis.

The association between POD24 status and OS was analyzed using a landmark with the event (for progressive patients within 24 months) or 24 months from trial registration (for non-POD24 patients) as a starting point for survival curves. A comparison of post-relapse OS between early (within 24 months from trial registration) and late relapse (i.e., relapsing after 24 months) using a Cox proportional hazards model was performed. Finally, to avoid the impact of immortality bias, a landmark analysis was used to evaluate the association of POD24 and OS for patients still alive at 24 months after trial registration.

Logistic regression models stratified on the study were used to evaluate the association between clinical or pathological variables at diagnosis and POD24 status. Baseline factors considered for inclusion in this model include independently the variables of the Mantle Cell Lymphoma International Prognostic Index [MIPI] (age, performance status (ECOG), leukocyte count and quotient of lactate dehydrogenase (LDH)/Upper Limit Normal (ULN)) as well as sex, Ann Arbor (AA) stage, presence of B symptoms, lymphocyte count and blastoid variant. Ki-67 index data was missing for 398 patients (31%), histological variant data was missing for 381 patients (30%), and multiple imputation ($n = 100$) was used for these variables. Baseline characteristics of patients with and without Ki-67/histological variant data were compared to build the imputation model based on sex, age, presence of B symptoms, quotient of LDH/ULN, leukocytes, lymphocytes, performance status (ECOG), study type, and POD24 status. The study type was included as a stratification factor in the models to consider potential additional differences between studies involved in this analysis. For each subgroup analysis, all baseline variables associated with POD24 in univariate analysis ($P \leq 0.20$) were included in a backward stepwise logistic regression model. Interaction between factors included in the final multivariable analyses were tested and were non-significant. To avoid bias of immortality, intensification/autologous stem cell transplantation (ASCT) and anti-CD20 maintenance strategies were analyzed in responding patients after induction only. Furthermore, to limit the bias related to ASCT eligibility and more particularly age, association between ASCT and POD24 was evaluated in the sub-population of 60–70 years old responding patients. Finally, the impact of anti-CD20 maintenance was analyzed in the population of patients that received an ASCT. Datasets without imputation were used in the final POD24 prediction model as sensitivity analyses. A P value of <0.05 was considered to denote statistical significance.

RESULTS

Patient characteristics and cumulative incidence of relapse

We analyzed data from 1386 patients included in six randomized trials. Four patients without progression-free survival (PFS) information available were excluded from this analysis (Fig. 1). Cumulative incidence of progression/relapse showed an incidence of 7% at 6 months, 13% at 12 months, 19% at 18 months and 22% at 24 months after trial registration. The slope of the curve showed an approximately linear association within 24 months of MCL diagnosis, while it became flat thereafter, with a point of inflection located around 24 months (Fig. 2A). We therefore used 24 months as the most appropriate cutoff for further analysis. One hundred and two patients were excluded from this study because they were censored for clinical follow-up before 24 months. Of the 1280 patients, 22.1% ($n = 283$) progressed, and 1.3% ($n = 16$) died due to lymphoma within 24 months of trial registration, leading to a total of 299 patients with POD24 status (23.4%) and 981 without disease-related events within 24 months. The median follow-up for these 1280 patients was 69.8 months. Most patients received CHOP-like (54%) or high-dose cytarabine-based regimen (35%) at induction.

Overall survival according to POD24 status

Patients with a POD24 event had a post-event median OS of 9.3 months (95% CI 8.4–11.8) whereas those without POD24 event had a median not reached OS (95% CI 97.8–NR; hazard ratio [HR] = 11.02; 95% CI 8.98–13.51; $P < 0.001$) (Fig. 2B). Importantly, only 27% of POD24 patients were alive 2 years after POD24 event, whereas 79% of non-POD24 patients were alive 7 years after trial registration (or five years after censored time). Among the deceased patients ($n = 406$), 68% ($n = 277$) of deaths were due to lymphoma and 32% ($n = 129$) of deaths due to other causes. Given the linear incidence of relapse, we looked at post-relapse OS according to early or late event status, using 24 months as cutoff. Among 981 non-POD24 patients, 314 (32%) presented a late lymphoma-related event. Median post-relapse OS of patients with a late relapse was 49.4 months (95% CI 30.4–56.8), significantly longer than post-relapse OS of POD24 patients (9.3 months, 95% CI 8.4–11.8; HR = 0.39; 95% CI 0.31–0.48; $P < 0.001$) (Fig. 2C). Finally, patients who progressed early but remained alive at

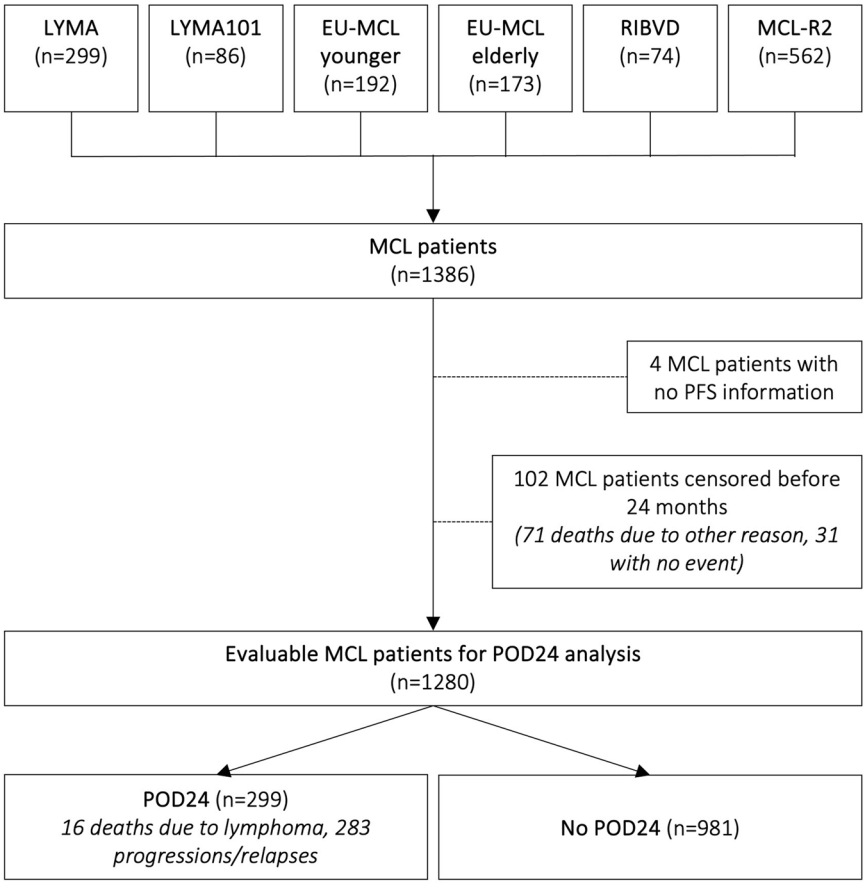

Fig. 1 Flowchart. Flowchart showing the number of patients included in the referenced randomized clinical trials and eligible for analysis in this study.

24 months after trial registration had 3- and 5-year survival probabilities of 64.8% and 40.2%, respectively, versus 96.2% and 87.8% for those without POD24 events (HR = 7.24; 95% CI 5.5–9.5; $P < 0.001$). We then analyzed the impact of POD24 in two distinct periods: the "pre-BTKi era" and the "BTKi era". Patients whose progression, death, or last contact occurred before 2018—when BTK inhibitors became available and reimbursed in France—were categorized as part of the "pre-BTKi era", as they were not treated with ibrutinib or other BTKi at first relapse. The risk of death remains higher in POD24 patients compared to non-POD24 patients, even in the context of BTKi, the "BTKi era" in 2018 or after (Supplementary Fig. 1A, B). However, we observe that among POD24 patients, the risk of death is higher for those with a date of progression, death, or last contact before 2018 compared to those with a date of progression, death, or last contact in 2018 or later (Supplementary Fig. 1C).

Logistic prediction model for POD24 at diagnosis

Table 1 summarizes patient-level baseline characteristics classified by POD24 status. Compared to non-POD24 patients, POD24 patients were older, had more frequent: an AA stage IV disease; performance status >1; B symptoms; elevated LDH; high MIPI score (high-risk MIPI 61% vs. 29%; $P < 0.001$); higher leukocytes and lymphocytes counts; blastoid variant morphology and Ki-67 > 30% (45% vs. 23%; $P < 0.001$). Gender and incidence of bulky disease were similar between both groups. In a multivariable logistic regression model using data imputation of Ki-67 scoring and blastoid variant for missing data, age (continuous), poor performance status (> 1), presence of B symptoms, high LDH (continuous), high leukocytes count (continuous), blastoid variant (OR = 3.13; 95% CI 2.1–4.7) and Ki-67 > 30% (OR = 2.41; 95% CI 1.8–3.3) were associated with increased risk of progression before 24 months, whereas AA stage (I–II vs. III vs. IV) was not significantly associated with POD24 status (Table 2). Sensitivity analysis without data imputation confirms these results (Supplementary Table 3).

Given that clinical features associated with POD24 can have a prognostic value by themselves, we assessed the independence of POD24 status on OS prediction from risk-defining events in a multivariable model including performance status, age, B symptoms, leukocytes, lymphocytes, blastoid variant, Ki-67, and LDH/ULN. In this model, POD24 remained strongly prognostic after adjusting for baseline prognostic factors (HR = 8.74; 95% CI 6.8–11.3, Table 3). Again, a sensitivity analysis without data imputation confirms this result (Supplementary Table 4).

Among the 1280 patients, 564 (44%) had measurable MRD at the end-of-induction, derived from the LYMA, LYMA-101, and MCL-R2 studies. In this subgroup, a positive MRD (detected by q-PCR) was associated with an increased risk of progression within 24 months (OR = 1.92, 95% CI: 1.2–3.0, $P = 0.0042$). However, it is important to note that this analysis excludes approximately 15% of patients with non-informative MRD results, as well as those who were primary refractory and were not assessed at the end-of-induction. Consequently, MRD results were not included in the multivariate model.

Impact of ASCT and anti-CD20 maintenance on POD24 status in responding patients at end-of-induction

Among the 1105 responding patients at end-of-induction, 180 (16.3%, POD24 patients) presented an POD24 event and 925 (83.7%) had no disease-related event within 24 months of trial registration. Six hundred and sixty-one patients (66.1%) received an anti-CD20 maintenance and 339 (33.9%) did not.

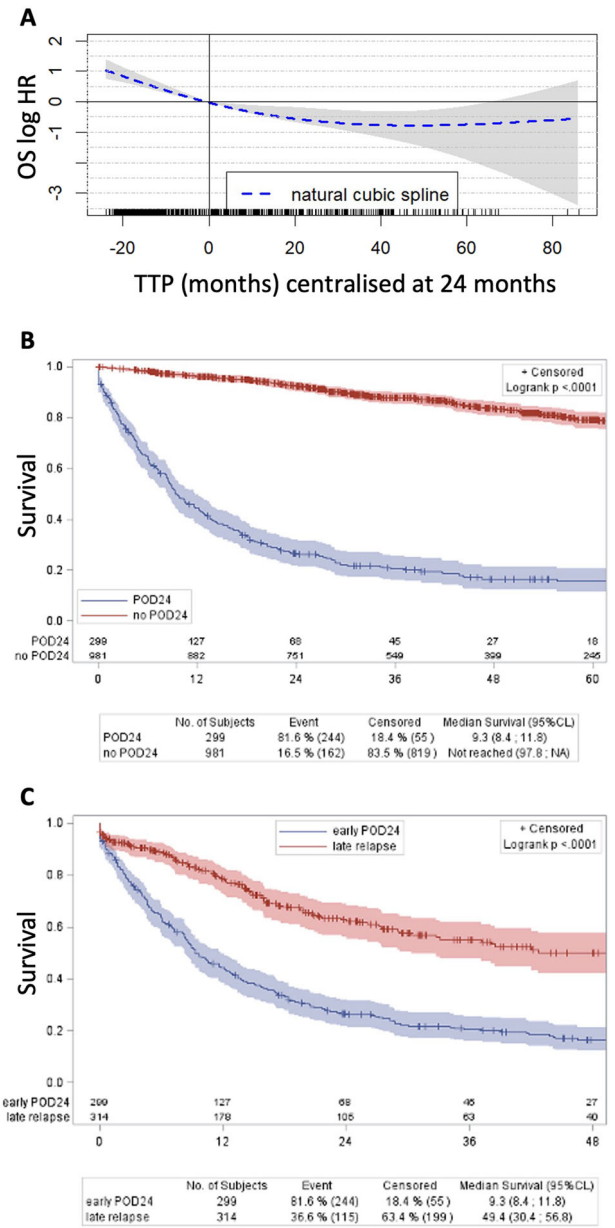

Fig. 2 Analysis of patients with mantle cell lymphoma experiencing first relapse or progression of disease (POD). Hazard model showing the relationship between risk of death from relapse or progression (Log relative hazard) and time to first relapse or progression (TTP) centralized at 24 months (for progressive patients only) (**A**); Overall survival according to POD24 status in the whole cohort, using a landmark with the event (for progressive patients) or 24 months (for non-POD24 patients) as a starting point for survival curves (**B**); Overall survival according to POD24 status in relapsing patient (**C**).

ASCT being only proposed to patients younger than 65 years old in LYMA/LYMA-101 and EU-MCL-young trials, its impact on the occurrence of POD24 in the global population cannot be assessed due to bias mainly related to age. However, we considered that conducting the analysis in the population of 60–70 years would reduce this age-related bias. Within the 451 patients aged 60–70 years old who were in response at end-of-induction, of which 159 received ASCT (35%), and 292 did not. Within ASCT patients, 16 (10%) subsequently had presented a POD24 event and 143 (90%) had no disease-related event within 24 months, whereas in the non-ASCT patients, 46 (16%) had presented a POD24 event (OR = 0.46; 95% CI 0.1–2.4). In a multivariable model including baseline clinical variables associated with POD24, ASCT was not significantly associated with POD24 (OR = 0.64; 95% CI 0.1–3.6), and only clinical variables (LDH, B symptoms, and Ki-67) remained significant.

Among responding patients presenting a POD24 event, 110/180 (61%) had received anti-CD20 maintenance, while within non-POD24 patients 551/925 (60%) had received anti-CD20 maintenance. In a multivariable model including baseline variables associated with POD24, as well as anti-CD20 maintenance, maintenance was associated with a decreased risk of progression within 24 months to the limit of significance (OR = 0.5; 95% CI 0.2–1.1) and clinical variables (age, LDH, and Ki-67) remained significant (Table 4).

Considering the potential bias related to ASCT in the global population, we assessed the potential impact of anti-CD20 maintenance on the risk of POD24 in the sub-population of patients that received an ASCT. Anti-CD20 maintenance was significantly associated with POD24 status (23% of POD24 patients received anti-CD20 maintenance vs. 43% for non-POD24, $P = 0.017$). In multivariable analysis including clinical covariates and anti-CD20 maintenance, maintenance was associated with the risk of POD24 (OR = 0.37; 95% CI 0.1–1.0) and clinical variables (age, LDH, leukocyte count, and Ki-67) remained significant (Table 5).

OS according to MIPI-combined score and POD24 status

Among the 875 patients with a MIPI-combined score available at trial registration, 161 (13%) had a high score and 87% a low or intermediate score. Among patients with a high MIPI-combined score, 86 (53%) presented a POD24 event, whereas 75 (47%) had no progression within 24 months after trial registration, versus 118 (17%) and 596 (83%) for patients with a low or intermediate MIPI-combined score (Supplementary Table 7). Importantly, the impact of MIPI-combined status on OS was significant in both POD24 and non-POD24 patients. Indeed, within POD24 patients, those with a high MIPI-combined score at diagnosis presented a worse OS than those with a low/int MIPI-combined score: 8 months vs. 13 months (HR = 1.80 95% CI: 1.3–2.5, $P = 0.0002$); within non-POD24 patients, the distinction was less obvious but remained significant (median OS of 65 months *vs.* not reached (HR = 2.52 95%CI: 1.5–4.2, $P = 0.0003$) (Supplementary Fig. 2).

DISCUSSION

To the best of our knowledge, this pooled analysis of 1280 patients included in six prospective clinical trials represents the largest cohort of MCL patients prospectively treated in the rituximab era. Using a modeling approach for time to progression and risk of death, we could confirm POD24 as a strong and robust indicator of poor survival in patients with MCL. The predictive power of OS was independent of age and other relevant clinical and pathological baseline risk factors. Patients experiencing an early event (23% of the population) had a post-event OS of 9 months and therefore can be considered the unmet medical need in MCL. On the other hand, in patients without a POD24 event, the outcome is excellent, even for those experiencing a late event. Age, performance status, LDH, B symptoms, leukocyte count, blastoid variant, and Ki-67 were independent baseline risk factors associated with the risk of POD24, suggesting that MIPI-combined score can be relevant for POD24 prediction, but also that pathological factors need to be considered. Within the population of patients aged 60–70 who responded at the end-of-induction, ASCT had no impact on the risk of early progression. Anti-CD20 maintenance provided significant protection against the risk of early progression, regardless of clinical risk factors and ASCT.

Table 1. Baseline characteristics and induction treatment according to POD24 status.

	POD24 ($n = 299$)	No POD24 ($n = 981$)	All patients ($n = 1280$)	*P* value
Gender—female	70 (23%)	257 (26%)	327 (26%)	0.364
Age (years)[a]	70 (63–74)	65 (57–71)	66.5 (59–72)	<0.001
Ann Arbor stage IV	271 (91%)	834 (85%)	1105 (86%)	0.049
ECOG > 1	45 (15%)	42 (4%)	87 (7%)	<0.001
MIPI				<0.001
Low	27 (9%)	333 (34%)	360 (28%)	
Intermediate	88 (30%)	360 (37%)	448 (35%)	
High	182 (61%)	281 (29%)	463 (36%)	
Presence of B symptoms	127 (43%)	251 (26%)	378 (30%)	<0.001
Elevated LDH	200 (67%)	336 (34%)	536 (42%)	<0.001
LDH (/upper normal limit)[a]	1.17 (0.9–1.6)	0.88 (0.7–1.1)	0.93 (0.8–1.2)	<0.001
Leukocytes (G/L)[a]	9.4 (6.1–18.5)	7.3 (5.7–10.3)	7.6 (5.8–11.5)	<0.001
Lymphocytes (G/L)[a]	2.0 (1.2–5.0)	1.9 (1.2–3.1)	2.0 (1.2–3.5)	0.033
Bulky disease[b]	32 (25%)	101 (21%)	133 (22%)	0.227
Blastoïd—yes[c]	49 (24%)	65 (9%)	114 (13%)	<0.001
Ki-67 > 30%[c]	134 (45%)	229 (23%)	363 (28%)	<0.001
Ki-67 (median)[c]	40 (21–61)	24 (13-36)	26 (15–41)	<0.001
MIPI-combined[c]				<0.001
Low	6 (3%)	177 (26%)	183 (21%)	
Low-intermediate	42 (21%)	234 (35%)	276 (32%)	
High-intermediate	70 (34%)	185 (28%)	255 (29%)	
High	86 (42%)	75 (11%)	161 (18%)	
Induction by high-dose cytarabine—yes	63 (21%)	385 (39%)	448 (35%)	<0.001

[a]Median (Q1–Q3); [b]50% missing data; [c]30% missing data.

Table 2. Logistic model for POD24 with baseline characteristics (all patients).

Variable	Modality	Model with imputation (OR (95% CI))
Age (years)	Continuous	1.041 (1.012–1.071)
Performance status	>1	2. 06 (1.2–3.5)
B symptoms	Yes	1.60 (1.2–2.2)
LDH/normal limit	Continuous	2.567 (1.94–3.39)
Leukocytes (G/L)	Continuous	1.004 (1.001–1.006)
Ki-67	>30%	2.41 (1.8–3.3)
Blastoid histology	Yes	3.13 (2.1–4.7)

Table 3. Cox model for OS from risk-defining events with baseline characteristics and POD24 (all patients).

Variable	Modality	Model with imputation (HR (95% CI))
POD24	Yes	8.74 (6.8–11.3)
Age	Continuous	1.034 (1.015–1.053)
Performance status	>1	1.59 (1.2–2.2)
LDH× normal limit	Continuous	1.048 (1.00–1.10)
B symptoms	Yes	1.50 (1.2–1.8)
Leukocytes	Continuous	1.006 (1.004–1.009)
Lymphocytes	Continuous	0.996 (0.992–0.999)
Ki-67	>30%	1.35 (1.0–1.7)
Blastoid	Yes	1.28 (0.92–1.8)

Table 4. Logistic model for POD24 with baseline characteristics and anti-CD20 maintenance (responding patients at end-of-induction only).

Variable	Modality	Model with imputation OR (95% CI)
Age	Continuous	1.058 (1.021–1.097)
LDH× normal limit	Continuous	2.268 (1.64–3.13)
Ki-67	>30%	2.57 (1.8–3.8)
Anti-CD20 maintenance	Yes	0.51 (0.2–1.1)

Table 5. Logistic model for POD24 with baseline characteristics and anti-CD20 maintenance (responding patients at end-of-induction and treated with ASCT).

Variable	Modality	Model with imputation OR (95% CI)
Age	Continuous	2.000 (1.0298–1.175)
LDH× normal limit	Continuous	2.195 (1.30–3.72)
Leukocytes	Continuous	1.005 (0.995–1.015)
Ki-67	>30%	3.95 (1.9–8.4)
Anti-CD20 maintenance	Yes	0.37 (0.1–1.0)

The prognostic impact of time to progression has already been studied in smaller retrospective studies in MCL patients treated in clinical trials [4] or in retrospective/ real-world analyses [15, 16, 23]. In these studies, the median OS after relapse ranged from 7 to

12 months, which is consistent with our results. Importantly, less than 25% of patients who progressed within 24 months of diagnosis were alive two years after relapse whereas almost 80% of non-POD24 patients were alive 7 years after registration in the trial. Among the baseline factors associated with POD24, Ki-67 is consistently reported, whereas using a multivariate model we showed that LDH, age, leukocyte count, B symptoms, performance status, and blastoid variant were also independently associated with the risk of POD24, suggesting that the MIPI-combined score by itself might not be sufficient to predict the risk of POD24. Given the independent value of the presence of blastoid variant and Ki-67 score, novel approaches, such as whole slide imaging and artificial intelligence algorithm, could be useful in risk stratification for MCL patients at diagnosis.

With the limitations of a retrospective analysis and patient selection bias, intensification and ASCT (in the population of patients aged 60–70 years old) did not significantly reduce the risk of early progression in responding patients. In line with these results, the role of ASCT in young MCL patients has recently been questioned by registry and prospective studies [24, 25]. On the contrary, patients receiving anti-CD20 maintenance post-ASCT had a lower incidence of POD24 events, consistent with the long-term results of LYMA and EU-MCL studies [2, 5]. Notably, this study includes trials, some of which were conducted before ibrutinib was approved for relapsing patients, a treatment known to offer better overall survival compared to other regimens [26].

As a limitation, we acknowledge the lack of *TP53* mutational status or immunohistochemistry data among the baseline characteristics. Risk stratification might be further improved by incorporating novel biological markers, such as *TP53* mutations [27, 28], P53 expression [29], *CDKN2A* deletion [30], *KMT2D* mutation [31], or genomic instability [32], however, beside *TP53* mutational status, none of these factors are routinely available and validated. As well, if we attempted to include treatment strategies in our model, using stepwise approach, and selecting specific populations, we do acknowledge the potential bias of these analyses, given that treatment decision relies on age in MCL.

Overall, our data position POD24 patients as the unmet medical need in MCL. Even though we identified clinical and biological baseline variables predictive of POD24 event in multivariable analysis, this remain to be validated in a large independent cohort to build a risk model at diagnosis. Whether this high-risk population includes homogenous biological features remain an open question and emphasize the need for biological characterization and strong but also routinely available biomarkers in order to guide future protocols. The addition of BTK inhibitor (ibrutinib) to induction improves the overall response rates and the PFS in untreated MCL patients [33–35] (Triangle, Shine, Echo, Enrich trials) and might reduce the risk of early progression, but the OS of patients refractory to these novel strategies remain unknown. In this moving field, the predictive value of POD24 for OS would have to be confirmed in the most recent clinical trials. More recently, several trials have been designed for so-called high-risk patients, but with different definition of inclusion criteria, such as *TP53* mutation (BOven study) [33], or P53 expression, combined with the MIPI-combined score. Which of these novel therapeutic approaches will reduce the incidence of POD24 must be proven in large cohorts with harmonized inclusion criteria.

Our study confirmed POD24 as a valid and robust prognostic factor of poor OS, among a large data set of MCL patients included in clinical trials, suggesting that it could be used as a primary endpoint in future clinical trials, thus allowing earlier evaluation and more adaptable design. While maintenance with rituximab seems to protect against the risk of early relapse, ASCT does not appear to have any impact on this risk, highlighting the need for alternative strategies.

REFERENCES

1. Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, et al. Treatment of older patients with mantle-cell lymphoma. New Engl J Med. 2012;367:520–31.
2. Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Geisler CH, Trneny M, et al. Treatment of older patients with mantle cell lymphoma (MCL): long-term follow-up of the randomized European MCL elderly trial. J Clin Oncol. 2020;38:248–56.
3. Hermine O, Jiang L, Walewski J, Bosly A, Thieblemont C, Szymczyk M, et al. High-dose cytarabine and autologous stem-cell transplantation in mantle cell lymphoma: long-term follow-up of the randomized mantle cell lymphoma younger trial of the European mantle cell lymphoma network. J Clin Oncol. 2023;41:479–84.
4. Eskelund CW, Dimopoulos K, Kolstad A, Glimelius I, Räty R, Gjerdrum L, et al. Detailed long-term follow-up of patients who relapsed after the Nordic mantle cell lymphoma trials: MCL2 and MCL3. HemaSphere. 2020;5:e510.
5. Sarkozy C, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Damaj G, et al. Long-term follow-up of rituximab maintenance in young patients with mantle-cell lymphoma included in the LYMA trial: a LYSA study. J Clin Oncol. 2023;42:769–73.
6. Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. New Engl J Med. 2017;377:1250–60.
7. Hermine O, Hoster E, Walewski J, Bosly A, Stilgenbauer S, Thieblemont C, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet. 2016;388:565–75.
8. Delarue R, Haioun C, Ribrag V, Brice P, Delmer A, Tilly H, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood. 2013;121:48–53.
9. Kolstad A, Laurell A, Jerkeman M, Grønbæk K, Elonen E, Räty R, et al. Nordic MCL3 study: 90Y-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma. Blood. 2014;123:2953–9.
10. Bommier C, Zucca E, Chevret S, Conconi A, Nowakowski G, Maurer MJ, et al. Early complete response as a validated surrogate marker in extranodal marginal zone lymphoma systemic therapy. Blood. 2024;143:422–8.
11. Casulo C, Dixon JG, Le-Rademacher J, Hoster E, Hochster HS, Hiddemann W, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood. 2022;139:1684–93.
12. Luminari S, Merli M, Rattotti S, Tarantino V, Marcheselli L, Cavallo F, et al. Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. Blood. 2019;134:798–801.
13. Epperla N, Welkie RL, Torka P, Shouse G, Karmali R, Shea L, et al. Impact of early relapse within 24 months after first-line systemic therapy (POD24) on outcomes in patients with marginal zone lymphoma: a US multisite study. J Hematol Oncol J Hematol Oncol 2023;16:49.
14. Dietrich S, Boumendil A, Finel H, Avivi I, Volin L, Cornelissen J, et al. Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol J Eur Soc Med Oncol. 2014;25:1053–8.
15. Visco C, Tisi MC, Evangelista A, Di Rocco A, Zoellner AK, Zilioli VR, et al. Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death. Br J Haematol. 2019;185:940–4.
16. Bond DA, Switchenko JM, Villa D, Maddocks K, Churnetski M, Gerrie AS, et al. Early relapse identifies MCL patients with inferior survival after intensive or less intensive frontline therapy. Blood Adv. 2021;5:5179–89.
17. Hoster E, Klapper W, Hermine O, Kluin-Nelemans HC, Walewski J, van Hoof A, et al. Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. J Clin Oncol J Am Soc Clin Oncol 2014;32:1338–46.
18. Hoster E, Rosenwald A, Berger F, Bernd HW, Hartmann S, Loddenkemper C, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European mantle cell lymphoma network. J Clin Oncol. 2016;34:1386–94.
19. Scheubeck G, Jiang L, Hermine O, Kluin-Nelemans HC, Schmidt C, Unterhalt M, et al. Clinical outcome of mantle cell lymphoma patients with high-risk disease (high-risk MIPI-c or high p53 expression). Leukemia. 2023;37:1887–94.
20. Le Gouill S, Beldi-Ferchiou A, Alcantara M, Cacheux V, Safar V, Burroni B, et al. Molecular response after obinutuzumab plus high-dose cytarabine induction for transplant-eligible patients with untreated mantle cell lymphoma (LyMa-101): a phase 2 trial of the LYSA group. Lancet Haematol. 2020;7:e798–e807.
21. Gressin R, Daguindau N, Tempescul A, Moreau A, Carras S, Tchernonog E, et al. A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for

first-line treatment of older patients with mantle cell lymphoma. Haematologica. 2019;104:138–46.
22. Ribrag V, Safar V, Kluin-Nelemans H, Oberic L, Feugier P, Casasnovas O, et al. Induction and maintenance therapy in elderly patients with mantle cell lymphoma: double-randomized MCL R2 elderly clinical trial by the European Mantle Cell Lymphoma Network. Blood. 2023;142:979.
23. Ekberg S, Glimelius I, Albertsson-Lindblad A, Weibull CE. Timing of disease progression and impact on survival in Swedish mantle cell lymphoma patients—a novel illness-death model study. Hematol Oncol. 2023;41:471–2.
24. Martin P, Cohen JB, Wang M, Kumar A, Hill B, Villa D, et al. Treatment outcomes and roles of transplantation and maintenance rituximab in patients with previously untreated mantle cell lymphoma: results from large real-world cohorts. J. Clin. Oncol. 2022;41:541–54.
25. Albertsson-Lindblad A, Palsdottir T, Smedby KE, Weibull C, Glimelius I, Jerkeman M. Survival in mantle cell lymphoma after frontline treatment with R-bendamustine, R-CHOP and the Nordic MCL2 regimen—a real world study on patients diagnosed in Sweden 2007-2017. Haematologica. 2022;107:740–3.
26. Malinverni C, Bernardelli A, Glimelius I, Mirandola M, Smedby KE, Tisi MC, et al. Outcomes of younger patients with mantle-cell lymphoma experiencing late relapse (>24 months): the LATE-POD study. Blood. 2024;144:1001–9. 2023023525
27. Eskelund CW, Dahl C, Hansen JW, Westman M, Kolstad A, Pedersen LB, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130:1903–10.
28. Carras S, Torroja A, Emadali A, Montaut E, Daguindau N, Tempescul A, et al. Long-term analysis of the RiBVD phase II trial reveals the unfavorable impact of TP53 mutations and hypoalbuminemia in older adults with mantle cell lymphoma; for the LYSA group. Haematologica. 2024;109:1857–65.
29. Aukema SM, Hoster E, Rosenwald A, Canoni D, Delfau-Larue MH, Rymkiewicz G, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. Blood. 2018;131:417–20.
30. Delfau-Larue M-H, Klapper W, Berger F, Jardin F, Briere J, Salles G, et al. High-dose cytarabine does not overcome the adverse prognostic value of CDKN2A and TP53 deletions in mantle cell lymphoma. Blood. 2015;126:604–11.
31. Ferrero S, Rossi D, Rinaldi A, Bruscaggin A, Spina V, Eskelund CW, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. Haematologica. 2020;105:1604–12.
32. Nadeu F, Martin-Garcia D, Clot G, Díaz-Navarro A, Duran-Ferrer M, Navarro A, et al. Genomic and epigenomic insights into the origin, pathogenesis, and clinical behavior of mantle cell lymphoma subtypes. Blood. 2020;136:1419–32.
33. Dreyling M, Doorduijn J, Giné E, Jerkeman M, Walewski J, Hutchings M, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403:2293–06.
34. Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. New Engl J Med. 2022;386:2482–94.
35. Lewis DJ, Jerkeman M, Sorrell L, Wright D, Glimelius I, Pasanen A, et al. Ibrutinib-rituximab is superior to rituximab-chemotherapy in previously untreated older mantle cell lymphoma patients: results from the International Randomised Controlled Trial, Enrich. Blood. 2024;144:235.

ACKNOWLEDGEMENTS

The authors thank all the patients, families, and caregivers who participated in the study. They also acknowledge LYSARC (The Lymphoma Academic Research Organisation) for funding the study, conducting the analysis, and every research team and nurse in the participating centers. The authors also thank all the investigators and the investigating centers.

AUTHOR CONTRIBUTIONS

MC, CS, LC, and OH conceptualized, supervised the study and wrote the manuscript. All authors (MC, CS, LC, VR, RG, CHG, HCK, CT, FM, FL, VS, BT, LO, GD, HG, KB, ROC, RH, WK, BB, CP, MHD, EAM, MC, MJ, MU, EH, MD, SLG, and OH) provided data and data analysis. LC performed statistical analysis. All authors (MC, CS, VR, RG, CHG, HCK, CT, FM, FL, VS, BT, LO, GD, HG, KB, ROC, RH, WK, BB, CP, MHD, EAM, MC, MJ, MU, MD, SLG, and OH), except LC and EH provided clinical care for the patients described. All authors (MC, CS, LC, VR, RG, CHG, HCK, CT, FM, FL, VS, BT, LO, GD, HG, KB, ROC, RH, WK, BB, CP, MHD, EAM, MC, MJ, MU, EH, MD, SLG, and OH) edited and approved the final version of the paper. MC, CS, and OH were responsible for the final version of the manuscript.

FUNDING

The authors thank CALYM for the financial support for this study.

COMPETING INTERESTS

MC reports honoraria from Amgen, CSL Behring, Astra Zeneca, Lilly, and Abbvie; research funding from Innate Pharma, Force Hemato, and Servier; travel and accommodation expenses from Pfizer, Griffols, CSL Behring, Astra Zeneca, Lilly, and Gilead but no competing financial interests for this study. FM reports consultancy for Roche/Genentech; and advisory boards for Roche, BMS, Gilead, Novartis, Epizyme, Genmab, AbbVie, and Kymera. VS reports consultancy for Kite/Gilead, Janssen; fundings from Janssen, Abbvie. The remaining authors declare no competing financial interests for this study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written informed consent was obtained from all participants, who were included in the previously published clinical trial (EU-MCL younger [7] NCT00209222, LyMA [6] NCT00921414, LyMA101 [20] NCT02896582, EU-MCL elderly [1] NCT00209209, RiBVD [21] NCT01457144 and MCL-R2 [22] NCT01865110). The studies were approved by an independent ethics committee and conducted in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01241-9.

Correspondence and requests for materials should be addressed to Morgane Cheminant.