

2017-08-18

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<http://hdl.handle.net/10026.1/10064>

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10.1111/bjh.14870

British Journal of Haematology

Wiley

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**Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies**

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**Running head:** Ibrutinib-treated patients with MCL

**Word count:**

Text: 2943 words

Abstract: 249 words

Tables/Figures: 1 table/5 figures

References: 31

Supplemental files: 1

## ABSTRACT

Mantle cell lymphoma (MCL) is a rare, aggressive B-cell lymphoma. Ibrutinib (first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase) is highly active in MCL. We pooled data from three ibrutinib studies to explore impact of baseline patient characteristics on response. Patients with relapsed/refractory MCL received once-daily ibrutinib 560 mg until progressive disease/unacceptable toxicity. ORR ( $n = 370$ ) was 66% (20% CR; 46% PR); median DOR, PFS, and OS were 18.6, 12.8 and 25.0 months, respectively. In CR patients, 79% were progression-free and 92% were alive at 2 years. Univariate analyses showed patients with one versus >one prior line of therapy had significantly longer OS. Multivariate analyses identified one prior line of therapy as affecting PFS and ECOG, and sMIPI, bulky disease, blastoid histology as affecting OS and PFS. Patients with blastoid *versus* non-blastoid histology had similar time to best response (2.2 vs. 2.1 months), but lower ORR (50.0% vs. 67.8%), DOR (8.6 vs. 18.8 months), PFS (5.1 vs. 14.6 months). OS (12.8 vs. not reached at 24 months) was significantly shorter in blastoid patients. PFS was significantly improved in patients with one versus >one prior line of therapy. OS and PFS were significantly longer in patients with better sMIPI scores, patients in ECOG performance status 0–1, non-bulky disease, and non-blastoid histology. Multivariate analyses indicated poor prognostic factors adversely impact OS. Additionally, proportions of patients with poor prognostic factors increases with increasing lines of therapy. Together, results suggest patient outcomes following treatment failure with ibrutinib are related to natural biologic evolution of the disease.

**Keywords:** ibrutinib, mantle cell lymphoma, pooled analysis.

## Introduction

Mantle cell lymphoma (MCL) is a rare, clinically aggressive B-cell lymphoma that accounts for 6–8% of all non-Hodgkin lymphoma (Dreyling *et al*, 2014). It is a disease that predominantly affects older men (median age of 65 years), usually presents as late-stage disease and is associated with a poor prognosis (Dreyling *et al*, 2016). The median overall survival (OS) of patients with MCL is 4–5 years (Herrmann *et al*, 2009; Smith *et al*, 2015). The majority of patients respond to initial therapy but then relapse. Following progression, subsequent treatment is often ineffective and survival is short (Herrmann *et al*, 2009).

Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton's tyrosine kinase (BTK). BTK is a member of the cytoplasmic tyrosine (Tec) kinase family and is important for signaling *via* B-cell receptors and other B-cell surface receptors (Khan, 2012). Ibrutinib binds in a potent and covalent manner to a cysteine residue (Cys-481) in the active site ATP-binding domain of BTK. This binding inhibits B-cell receptor signalling within the malignant B-cell, leading to downstream mitigation of cell growth, proliferation, survival, adhesion, and migration (Buggy & Elias, 2012; Cinar *et al*, 2013; de Rooij *et al*, 2012; Herman *et al*, 2011; Honigberg *et al*, 2010; Ponader *et al*, 2012; Cheng *et al*, 2014). Based on the results of a phase II study (PCYC-1104) in patients with relapsed or refractory (R/R) MCL, ibrutinib was approved in the United States, the European Union, and elsewhere around the world for patients with MCL who have received at least one prior line of therapy (Wang *et al*, 2013).

Two additional studies have been reported with ibrutinib in patients with R/R MCL: the phase II MCL2001 (SPARK) (Wang *et al*, 2014) and phase III MCL3001 (RAY) (Dreyling *et al*, 2016) studies. In both of these studies, a high overall response rate (ORR) was seen, which appeared to be largely independent of traditional poor-risk prognostic factors associated with this disease. Recent reports (Cheah *et al*, 2015; Martin *et al*, 2016) suggest that outcomes

following ibrutinib progression may be poor, but the key question that remains is whether this is due to a biologic effect of ibrutinib or to the disease biology of the patient population itself. Interestingly, other studies (Dreyling *et al*, 2016; Rule *et al*, 2015) suggest that post-progression outcomes in ibrutinib-treated patients are less negatively affected, with significantly longer progression-free survival 2 (PFS2) with ibrutinib versus temsirolimus. This indicates that improvement with ibrutinib is preserved following post-progression treatments. Another major finding of this study is that within the ibrutinib-treated cohort, PFS is longer in patients treated with one *versus* more than one prior line of therapy (Fig S1) (Rule *et al*, 2015).

In this analysis, we pooled patient-level data from three single-agent ibrutinib studies, PCYC-1104, SPARK and RAY (ibrutinib-treated cohort), to further characterize the efficacy profile of single-agent ibrutinib in MCL and to assess the best potential place for its use in patients with R/R MCL. In particular, an improved understanding of the baseline factors influencing outcomes may provide guidance to help determine the optimal clinical use of ibrutinib.

## Methods

Patients with R/R MCL enrolled in three separate studies, PCYC-1104, SPARK and RAY (ibrutinib arm only), and received ibrutinib 560 mg orally once daily until progressive disease or unacceptable toxicity. Inclusion and exclusion criteria were similar in all three studies; however, SPARK required patients to have received prior rituximab and bortezomib, and RAY required patients to have received prior rituximab. For further details on eligibility criteria, please refer to the individual studies (PCYC-1104 (Wang *et al*, 2013); SPARK (Wang *et al*, 2014); RAY (Dreyling *et al*, 2016)). Blastoid histology was not centrally reviewed but was investigator-categorized at baseline. All patients provided written informed consent. Patient-level data from these studies were integrated for analyses. In addition to descriptive statistics for both efficacy

and safety parameters, exploratory analyses were conducted using Kaplan-Meier estimates for efficacy endpoints PFS and OS. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using both univariate and multivariate Cox regression model. Common prognostic factors that were deemed to have prognostic value ( $P < 0.1$ ) in the univariate analysis and were collected in all three studies were included as covariates in a multivariate Cox model adjusted by study. The multivariate Cox regression adjusted by study included the following covariates: age, extra nodal disease, Eastern Cooperative Oncology Group (ECOG) performance status, simplified MCL international prognostic index (sMIPI) risk, prior lines of therapy, bulky disease, blastoid histology and bone marrow involvement. ORR was presented over time and by prior lines of therapy. Best overall response was summarized by patient baseline characteristics. Common treatment-emergent adverse events (AEs) ( $\geq 10\%$  of patients) were summarized by preferred terms and toxicity grades.

## Results

The baseline demographic and disease characteristics of the individual ibrutinib-treated populations (PCYC-1104,  $n = 111$ ; SPARK,  $n = 120$ ; RAY,  $n = 139$ ) were generally comparable, although the PCYC-1104 population had a slightly higher proportion of patients with intermediate/high-risk MCL (86% vs. 76% in SPARK and 69% in RAY). Full baseline characteristics for patients in each trial and for the pooled population ( $n = 370$ ) are shown in Table S1.

Trial outcomes were similar between PCYC-1104, SPARK, and RAY, respectively: ORR was 68%, 63% and 72%; median PFS was 13.9, 10.5 and 14.6 months; median OS was 22.5 months, 25.4 months and not reached; and estimated OS at 18 months was 58%, 61% and 58%. Median duration of follow-up for PCYC-1104, SPARK and RAY was 15.5, 14.9 and 20 months, respectively.

For the pooled population, the median age was 67.5 years, with patients having received a median of two prior lines of therapy. Seventy-six percent of patients had intermediate/high-risk sMIPI and 49% had bulky disease (longest diameter  $\geq 5$  cm). The overall median treatment duration across the three studies was 11 months, with a median dose intensity of 98.4%, and the median duration of follow-up was 24–25 months. Thirty-five percent of patients were still on therapy at 18 months. The median PFS of the overall MCL population was 12.8 months and median OS was 25.0 months (Fig 1). The median (range) time to first response and best response were 2.07 (0.53–13.73) and 2.14 (0.53–24.74) months, respectively.

Overall, the most common sites of progression were the lymph nodes, with the mediastinum, external iliac, and abdominal sites most commonly involved (37%, 35% and 32% of progressed patients, respectively). Extranodal sites that were commonly involved at progression were the liver, lung, and gastrointestinal tract (34%, 23% and 20% of progressed patients, respectively). In total, four (3.1%) patients showed central nervous system (CNS) involvement at progression in this poor risk patient cohort (e.g., high sMIPI, 32% of patients, high lactate dehydrogenase [LDH] 54% of patients).

PFS and OS were markedly different in patients based on the number of previous lines of therapy. Patients who had received only one prior line of therapy had the longest PFS and OS (median not reached), and 2-year PFS and OS estimates were 57% and 68%, respectively (Fig 2).

ORRs and complete response (CR) rates improved over time (Fig S2A). Overall, almost one-third of responders achieved a CR, with an overall CR rate of 20% and partial response (PR) rate of 46%. Response rates also differed based on the numbers of prior lines of treatment (Fig S2B), non-refractory status, and low sMIPI risk scores. For prior lines of treatment, patients



treated with ibrutinib at second line achieved the highest ORR and CR rate (73% and 27%, respectively) (Fig S2B). The depth of response markedly affected long-term outcomes; patients who achieved a CR exhibited the longest PFS and OS (Fig 3): median PFS and OS were not reached and with landmark rates of PFS and OS at 2 years of 79% and 92%, respectively.

ORR (Table SII) was summarized by baseline characteristics. PFS and OS were explored in a univariate non-stratified Cox regression model by fitting baseline prognostic factors (Fig 4 and Fig S3). PFS and OS outcomes demonstrated similar trends regarding patient outcomes by baseline characteristics. Prior bortezomib did not appear to have any effect on PFS or OS. Trends toward a difference in outcomes were observed with regard to refractory status, disease stage and prior transplant; however, these did not reach statistical significance. Baseline characteristics such as age, ECOG performance status, sMIPI risk, prior lines of therapy, bulky disease, bone marrow involvement, beta-2 microglobulin (B2M) levels, normal LDH and blastoid histology did show statistical significance (Fig 4 and Fig S3).

Better outcomes were associated with younger age, ECOG performance status 0–1, lower sMIPI score, fewer prior lines of therapy, normal LDH levels, lower B2M and non-bulky disease or non-blastoid histology (Fig 5 and Fig S4). Patients with blastoid and non-blastoid histology had an ORR of 50.0% and 67.8% and time to best response of 2.2 and 2.1 months, respectively; however, duration of response (DOR) (8.5 vs. 18.8 months), PFS (5.1 vs. 14.6 months), and OS (12.8 vs. not reached at 24 months) were significantly shorter in patients with blastoid histology.

Additional exploratory analyses of PFS and OS were performed using a selected set of prognostic variables in a multivariate, Cox regression model adjusted by study. The model revealed that ECOG performance status, sMIPI, bulky disease and blastoid histology

significantly affect both PFS and OS, suggesting that each of these factors independently drives outcomes. As the multivariate analysis was only significant for PFS for one versus more than one prior line of therapy, these results suggest that ibrutinib, independent of baseline factors, significantly improves PFS in those patients who receive ibrutinib earlier versus later (Table I).

Treatment-emergent AEs were reported in 364 (98.4%) patients in the MCL pooled population. Grade  $\geq 3$  AEs were reported in 265 (71.6%) patients. The most frequently reported AEs (any grade) were diarrhoea ( $n = 146$ , 39.5%), fatigue ( $n = 129$ , 34.9%), cough ( $n = 81$ , 21.9%), nausea ( $n = 80$ , 21.6%), peripheral oedema and thrombocytopenia (both  $n = 74$ , 20.0%) (Table SIII). Other AEs of clinical interest occurred in a minority of patients, including grade  $\geq 3$  atrial fibrillation in 17 (4.6%) patients, and grade  $\geq 3$  major bleeding in 18 (4.9%) patients. Rash occurred in 57 (15.4%) patients. The incidence of other malignancies was 5.7% in the overall population, the majority of which (67%) were non-melanoma skin cancers.

## Discussion

Outcomes are poor for patients with MCL who relapse after initial therapy. Until recently, limited treatment options have been available. New targeted therapies in the last decade have been added to our armamentarium (e.g., bortezomib, lenalidomide and temsirolimus). These agents have activity, but the majority of patients do not respond well and responses are often short-lived. Ibrutinib was licensed by the US Food and Drug Administration in February 2013, based on phase II data in a single-arm study (PCYC-1104) (Wang *et al*, 2013). The results observed with ibrutinib showed ORR and CR rates higher than what had previously been seen with any other single agent (Fisher *et al*, 2006; Hess *et al*, 2009; Trneny *et al*, 2016). These results were confirmed in two subsequent studies (Dreyling *et al*, 2016; Wang *et al*, 2014). The phase III RAY study randomized patients to ibrutinib or temsirolimus and demonstrated a significant improvement in both ORR and PFS in favour of ibrutinib.

The pooled analysis confirms that response rates are consistently high across all the different subgroups examined, but PFS and OS are dependent on baseline characteristics. Both univariate and multivariate Cox regression models show similar and consistent results; together, these analyses indicate that blastoid histology, sMIPI, bulky disease and ECOG performance status remain prognostic in terms of PFS and OS with ibrutinib.

The pooled analysis allows us to look specifically at patients with blastoid histology ( $n = 44$ ). The ORR was 50% in patients with blastoid histology ( $n = 44$ ); however, both PFS and OS were shorter than in patients with non-blastoid histology. This is consistent with outcomes observed with other treatments in blastoid MCL (Bhatt *et al*, 2016). In the pooled analysis, 50% of patients with blastoid histology achieved an objective response and best response within 2 to 3 months, with a median DOR of 8 months, suggesting that consolidation of a response with bone marrow transplant should optimally be performed within 5 to 6 months of starting ibrutinib therapy.

Results from exploratory analyses of ibrutinib in chronic lymphocytic lymphoma suggest that PFS and OS outcomes may improve when ibrutinib is used earlier in treatment (Brown *et al*, 2014; Burger *et al*, 2015). A similar exploratory analysis was conducted in the ibrutinib phase III MCL study (Rule *et al*, 2015), which suggested the same improvement in outcomes (Fig S1). The pooled analysis confirms this finding with patients shown to have significantly longer PFS and OS when ibrutinib was used after initial relapse versus later in treatment. These results were further validated in the multivariate analysis when identifying line of therapy as an independent factor for PFS.

In the phase III RAY study, analysis of PFS2 (defined as time to progressive disease after next line of therapy, death or start of second subsequent therapy) (Dreyling *et al*, 2016) show that post-progression outcome is poor, independent of prior ibrutinib exposure. In combination with

those findings, the current results indicate that disease characteristics and line of therapy independently impact outcomes with ibrutinib. These findings suggest that the dismal outcomes reported after ibrutinib treatment (Cheah *et al*, 2015; Martin *et al*, 2016) are attributable mostly to adverse disease characteristics. This is further supported by the analysis showing that the proportion of patients with poor prognostic factors increases with increasing lines of therapy (Fig S5).

One important finding from this analysis is that the DOR observed with ibrutinib is proportionate to the depth of that response. In patients who achieved a CR with ibrutinib, 70% were progression-free and 90% were alive at 2 years. These data would support the concept of combination regimens involving ibrutinib in an attempt to maximize the CR rate. In R/R MCL, Maddocks *et al*. (Maddocks *et al*, 2015) previously reported a 94% ORR and 76% CR rate with ibrutinib in combination with bendamustine/ rituximab. Prior studies on bendamustine/ rituximab (without ibrutinib) demonstrated an ORR/CR of 97%/31% (Flinn *et al*, 2014) and 82%/40% (Czuczman *et al*, 2015). Wang *et al*. (Wang *et al*, 2016) reported an 88% ORR and 44% CR rate with ibrutinib plus rituximab. It is unknown whether the PFS and OS rates of the patients who achieved CR are similar to those observed in the current pooled analysis. However, this will likely be further addressed in the upcoming SHINE phase III study (NCT01776840), in which ibrutinib or placebo are being combined with bendamustine and rituximab in treatment-naïve patients aged  $\geq 65$  years who are not eligible for transplant.

Clinical reports have recently shown that ibrutinib can penetrate into the CNS, with clinical responses reported in patients with Bing-Neel syndrome (Cabannes-Hamy *et al*, 2016) and CNS responses reported in MCL patients (Bernard *et al*, 2015; Choquet *et al*, 2016; Grommes *et al*, 2016). Most patients in this pooled analysis had at least one risk factor for CNS involvement. In these patients, blastoid histology, the presence of B-symptoms, increased

serum LDH, ECOG performance status  $\geq 2$ , and a high sMIPI score are considered risk factors for CNS involvement during the course of the disease (Cheah *et al*, 2013); however, among patients who progressed in our pooled analysis, 3.1% showed involvement of the CNS. The role of ibrutinib in the treatment of patients with CNS lymphoma is being further explored in clinical studies.

While not the primary focus of this pooled analysis, it is important to comment that in MCL and other B-cell malignancies, the overall safety of ibrutinib indicates a favourable risk-benefit profile. No new safety signals were observed in any of these three studies, and all of the findings were consistent with the known safety profile of ibrutinib in clinical settings.

These results support the use of ibrutinib earlier in the treatment algorithm, with significant improvements in both PFS and OS when used at first relapse rather than later. It also seems that the poor prognostic factors that increase in later lines of therapy not only impact traditional chemotherapy but also ibrutinib outcomes. However, ibrutinib also appears to overcome some of the common poor risk factors such as refractory status and disease stage, and may even provide an important option for patients with blastoid histology, allowing them to bridge to therapies that may lead to better long-term outcomes. Overall, ibrutinib represents a significant advance in the treatment of this challenging lymphoma and further on-going studies will help define the optimal position in therapy as well as the best combination partner for ibrutinib.

### **Acknowledgements**

The authors would like to thank Michelle Olsher, PhD for writing assistance (PAREXEL, Hackensack, NJ, USA), funded by Janssen Global Services, LLC. We also thank the patients

who participated in this trial, their families, and the investigators and coordinators at each of the clinical sites. The investigators are listed in the supplemental material.

#### **Authorship Contributions:**

SR, MD, AG, GH, RA, BK, FC, JG, JV, MW and MW were responsible for study conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. NC was responsible for collection and assembly of data, data analysis, and interpretation, and manuscript approval. BL and DB were responsible for data analysis and interpretation, manuscript writing, and manuscript approval. SY was responsible for data analysis and interpretation and manuscript approval.

#### **Funding**

This study was funded by Janssen Research & Development. Funders were involved in the study design, data collection, data analysis and interpretation, and provided writing support. Lead investigators (SR, MW) had full access to the data and analyses for compilation of this report.

#### **Conflict of Interest Disclosures**

SR reports grants and personal fees from Janssen, during the conduct of the study; personal fees from Roche, personal fees from Pharmacyclics, personal fees from Celgene, outside the submitted work. MD reports grants and personal fees from Janssen, outside the submitted work. GH reports grants and personal fees from Roche, grants and personal fees from Pfizer, grants from CTI, personal fees from Janssen, grants and personal fees from Celgene, outside the submitted work. RA reports personal fees from Janssen, other from Janssen, non-financial

support from Janssen, personal fees from Bristol Myers Squibb, personal fees from Celgene, outside the submitted work. BK reports grants from Pharmacyclics, during the conduct of the study; personal fees from Gilead, personal fees from Infinity, personal fees from Pharmacyclics, outside the submitted work. NC, FC and DB are employees of Pharmacyclics. BL, SY, JG and MW are employees of Janssen Research & Development and hold stock in Johnson & Johnson outside the submitted work. JV is an employee of Janssen Biologics and holds stock in Johnson & Johnson outside the submitted work. AG and MW declare no competing interests.

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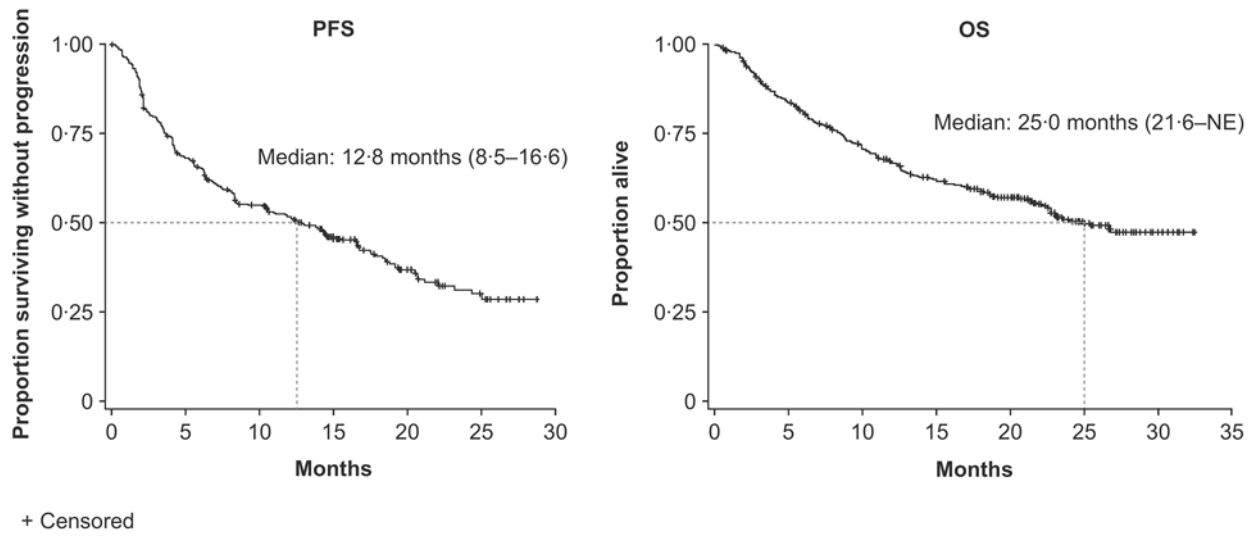
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**Table I.** Multivariate analysis of progression-free survival (PFS) and overall survival (OS).

	<b>PFS HR (95% CI)</b>	<b>P value</b>	<b>OS HR (95% CI)</b>	<b>P value</b>
<b>Age &lt;65 years</b>	0.988 (0.722–1.352)	0.9397	0.790 (0.549–1.137)	0.2041
<b>No extranodal disease</b>	0.804 (0.604–1.070)	0.1340	0.872 (0.633–1.201)	0.4013
<b>ECOG performance status 0–1</b>	<b>0.584 (0.359–0.949)</b>	<b>0.0299*</b>	<b>0.454 (0.263–0.782)</b>	<b>0.0045*</b>
<b>MIPI</b>				
<b>High risk</b>	<b>2.266 (1.431–3.589)</b>	<b>0.0005*</b>	<b>2.372 (1.401–4.016)</b>	<b>0.0013*</b>
<b>Intermediate risk</b>	<b>1.624 (1.081–2.440)</b>	<b>0.0195*</b>	<b>1.678 (1.046–2.692)</b>	<b>0.0319*</b>
<b>One prior line of therapy</b>	<b>0.651 (0.448–0.946)</b>	<b>0.0245*</b>	0.695 (0.459–1.055)	0.0873
<b>Non-bulky disease (&lt;5 cm)</b>	<b>0.703 (0.528–0.938)</b>	<b>0.0164*</b>	<b>0.608 (0.438–0.844)</b>	<b>0.0029*</b>
<b>Non-blastoid histology</b>	<b>0.442 (0.303–0.646)</b>	<b>&lt;0.0001*</b>	<b>0.397 (0.259–0.608)</b>	<b>&lt;0.0001*</b>
<b>No bone marrow involvement</b>	0.936 (0.709–1.236)	0.6411	0.733 (0.537–1.002)	0.0511
<b>Study 1104 (phase II)</b>	0.848 (0.589–1.223)	0.3779	0.757 (0.499–1.150)	0.1923
<b>Study 2001 (phase II)</b>	1.294 (0.914–1.831)	0.1465	0.924 (0.628–1.358)	0.6861

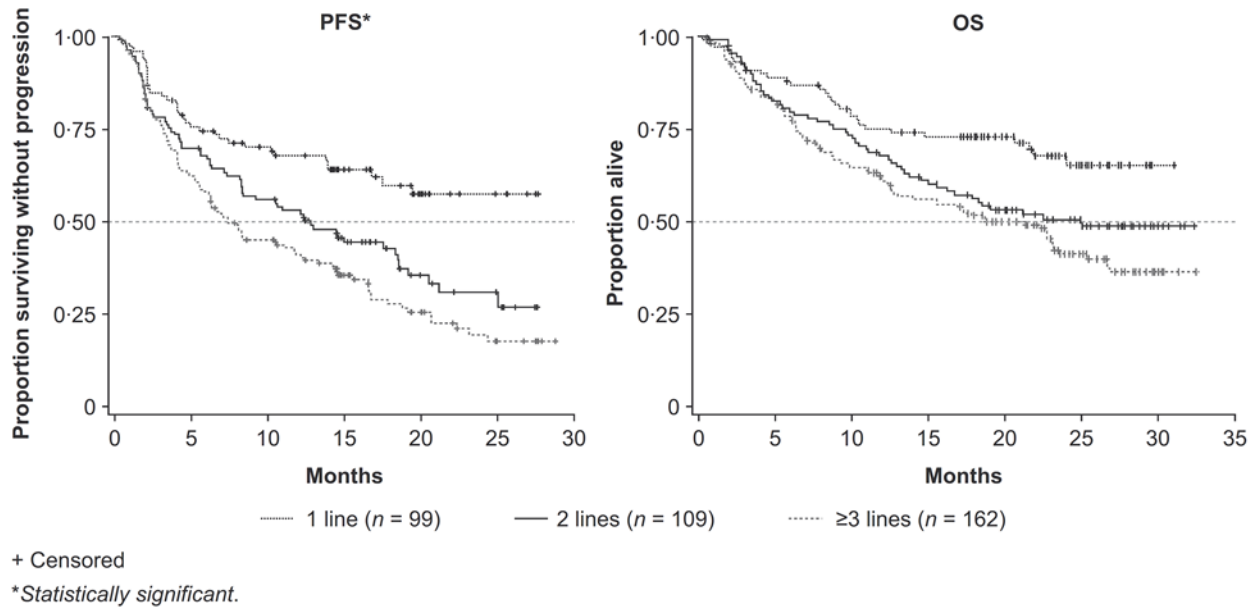
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MIPI, mantle cell lymphoma international prognostic index. \*Significant.

**Fig 1.** Progression-free survival (PFS) and overall survival (OS) for MCL pooled population.

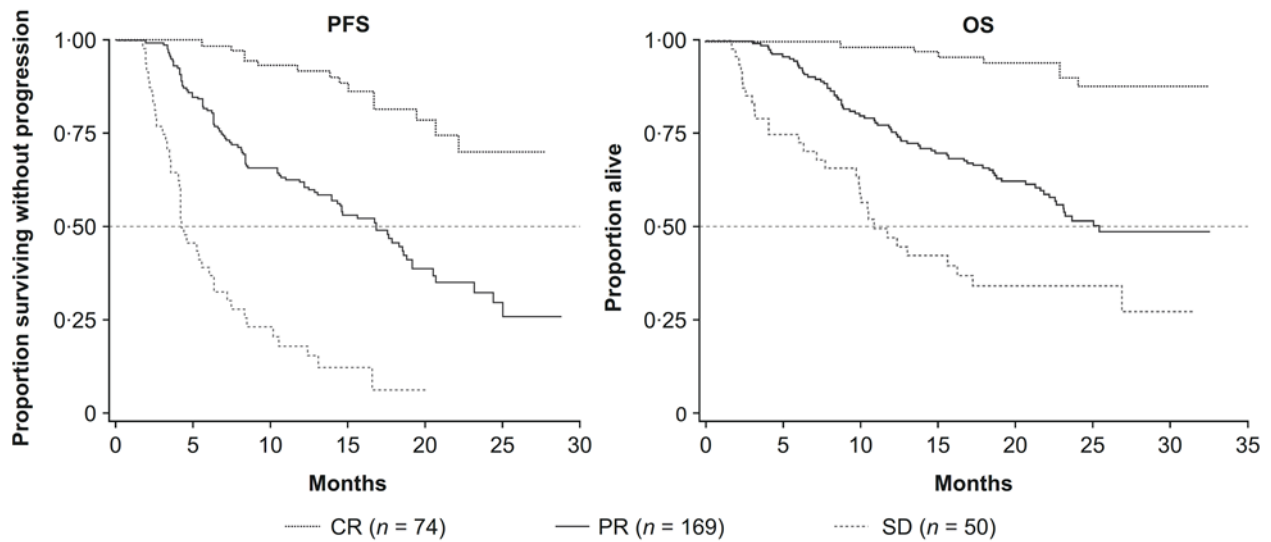




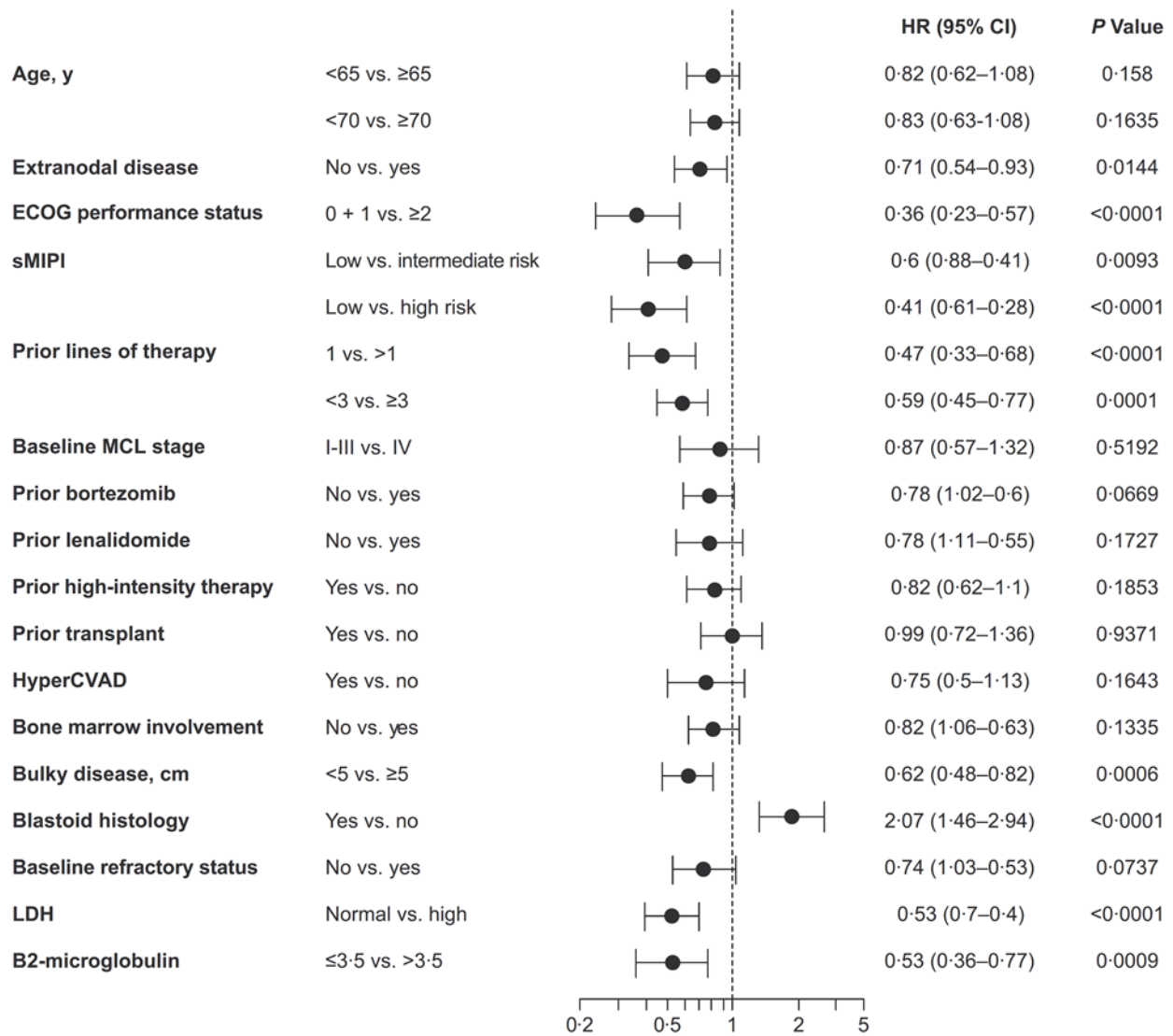
**Fig 2.** Progression-free survival (PFS) and overall survival (OS) by prior lines of therapy.



**Fig 3.** Progression-free survival (PFS) and overall survival (OS) by best response.



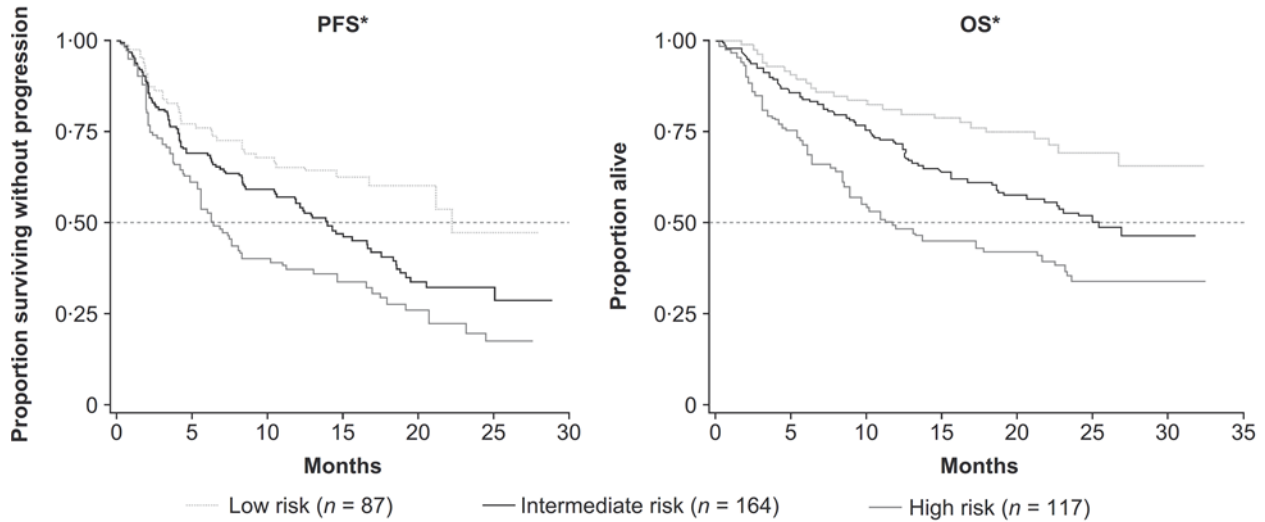
**Fig 4.** Forest plot of progression-free survival for pooled MCL analysis.



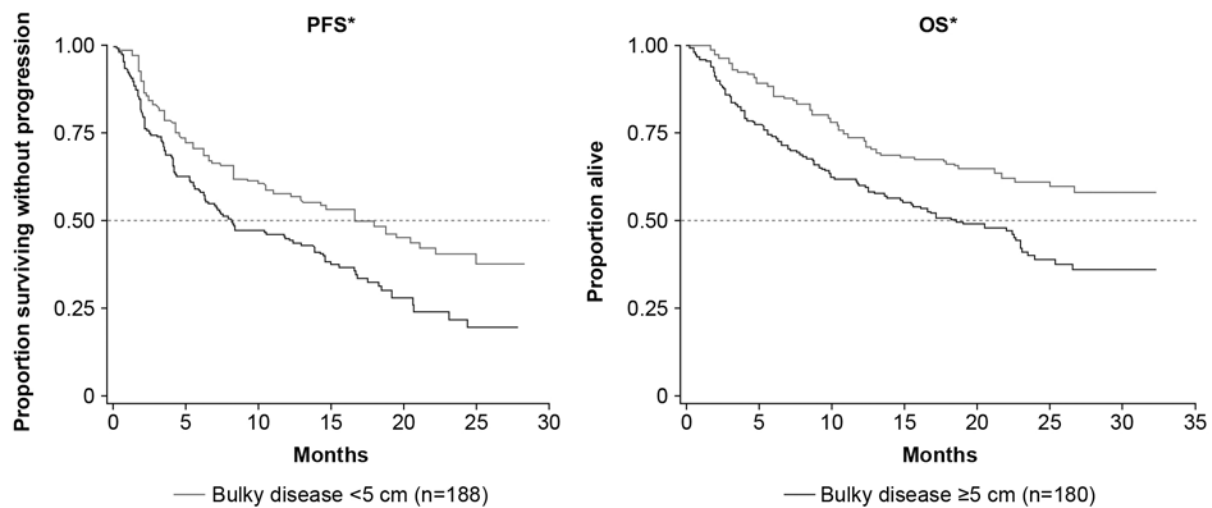
CI, confidence interval; CVAD, central venous access device; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; sMIPI, simplified MCL international prognostic index.

**Figure 5.** Progression-free survival (PFS) and overall survival (OS) by baseline factors: (A) simplified MCL international prognostic index (sMIPI), (B) bulky disease, and (C) blastoid histology.

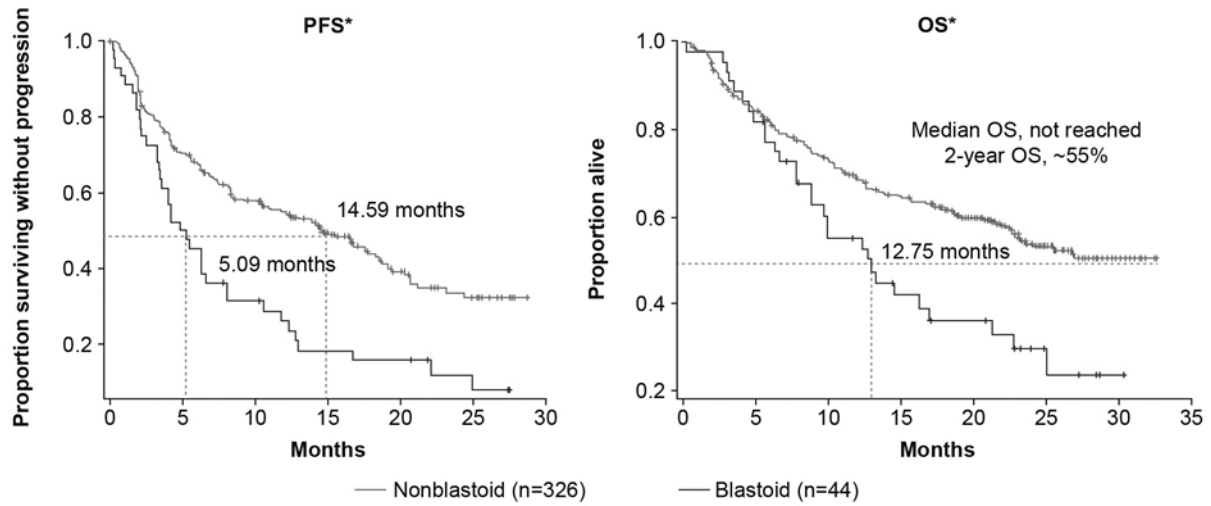
**(A)** sMIPI low vs. medium vs. high



**(B)** Bulky disease yes vs. no



**(C) Blastoid histology yes vs. no**



+ Censored

\*Statistically significant.