

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

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Abstract

Between 2011 and 2012, a phase II trial evaluated the use of the RiBVD (rituximab, bendamustine, velcade and dexamethasone) combination as first-line treatment for mantle cell lymphoma (MCL) patients over the age of 65. We have now re-examined the classic prognostic factors, adding an assessment of TP53 mutation status. Patients (N=74; median age 73 years) were treated with the RiBVD combination. Median progression-free survival (mPFS) was 79 months and median overall survival (mOS) was 111 months. TP53 mutation status was available for 54/74 (73%) patients. TP53 mutations (TP53mt) were found in 12 patients (22.2%). In multivariate analysis, among the prognostic factors (PF) evaluated, only TP53mt and an albumin level (Alb) 3.6 g/dL were independently associated with a shorter mPFS. A hazard ratio (HR) of 3.16 (1.3-9.9, $P=0.014$) was obtained for TP53mt versus TP53 wild-type (wt), and 3.6 (1.39-9.5, $P=0.009$) for Alb <3.6 g/dL versus Alb \geq 3.6 g/dL. In terms of mOS, multivariate analysis identified three PF: TP53mt (HR: 5.9 [1.77-19.5, $P=0.004$]), Alb <3.6 g/dL (HR: 5.2 [1.46-18.5, $P=0.011$]), and ECOG=2 (HR: 3.7 [1.31-10.6, $P=0.014$]). Finally, a score combining TP53 status and Alb distinguished three populations based on the presence of 0, 1, or 2 PF. For these populations, mPFS was 7.8 years, 28 months, and 2.5 months, respectively. Our prolonged follow-up confirmed the efficacy of the RiBVD regimen, comparing it favorably to other regimens. TP53mt and hypoalbuminemia emerge as strong PF that can be easily integrated into prognostic scores for older adult patients with MCL.

Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma characterized by the hallmark t(11;14)(q13;q32) chromosomal translocation that juxtaposes the CCND1 and IGH genes on the derivative chromosome 14, and triggers overexpression of the fusion protein.^{1,2} In addition to the t(11;14) translocation, the genetics of MCL are characterized by the occurrence of late complex secondary genomic events.³ Among these, TP53 alterations have emerged as a major unfavorable prognostic factor (PF) in MCL patients eligible for treatment with intensive therapies combining cytotoxic agents.⁴⁻⁷ However, in older patients, the impact of TP53 alterations remains less well characterized, partly due to a lack of large prospective studies.

Up to now, initial prognosis assessment has relied on clinical and biological parameters integrated into composite scores (Mantle Cell Lymphoma International Prognostic Index [MIPI], MIPIcombined, GOELAMS Index, etc.) to help define the risk of treatment failure. Nevertheless, these scores appear to work less well with older adult populations where high MIPI and MIPIb scores are over-represented, thus limiting their utility for risk stratification.^{8,9} Other PF have been proposed, such as complex karyotype, MYC rearrangement,^{10,11} alterations to KMT2D, CDKN2A, and SWI-SNF complex, or molecular signatures,^{7,12-14} but their usefulness with older adults remains unclear. It therefore appears important to identify new PF that can help guide therapeutic decisions related to novel, more effective, regimens for older adult subjects.

No satisfactory international consensus has yet been reached for first-line management of MCL in older adults or patients who are ineligible for high-dose treatment. However, the literature provides some hints to select combination therapy that should improve progression-free

survival (PFS).^{8,9,15-20} We previously reported the results of a RiBVD (rituximab, bendamustine, velcade and dexamethasone) regimen without rituximab maintenance (RM) which extended median PFS (mPFS) up to five years.¹⁶ These results illustrate the significant recent improvements in clinical management of MCL compared to the 30% complete remission (CR) rate and mPFS of less than two years reported in 2000-2010 when the R-CHOP regimen was first described.

In this paper, we present an analysis of the long-term follow-up of the RiBVD phase II trial (clinicaltrials.gov identifier: 01457144) and of the PF affecting long-term survival for MCL patients, including TP53 status.

Methods

The study was approved by institutional review boards and ethics committees at all sites, and conducted in line with the Declaration of Helsinki. The study design, patients' initial characteristics, treatment procedure, response assessment and minimal residual disease (MRD) analyses are all fully described in Gressin et al.¹⁶ Ki67 levels were assessed by immunohistochemistry (IHC) according to international recommendations.²¹ Staining for p53 was performed using an automated stainer (1:8000) (Automate Ventana Benchmark Ultra) with a mouse monoclonal antibody (Leica/NovoCastra clone DO7) diluted in a CC1 Tris-EDTA buffer, pH 7.8. p53 IHC was scored by visual inspection by two observers (BB and DC).²² Cases were scored on tissue microarrays (TMA) or whole slides depending on the type of sample.

As the study was initially designed to monitor patients for up to five years, the updated long-term results presented here were obtained from routine practice records (comprising both clinical, morphological and biological follow-up). Data were obtained for the last consultation

or based on the recorded date of relapse, confirmed by scan or biological assessment. The final completion date for data inclusion was July 1st 2022.

For molecular analysis, using QIAprep Miniprep (Qiagen, Valencia, CA, USA), DNA was extracted from paraffin-embedded biopsy samples using a Promega A1720 kit (Promega) or from invaded bone marrow (BM) and/or peripheral blood (PB) specimens collected before initiating treatment. Samples were analyzed using a commercial Ion Ampliseq panel (*TP53* panel #ID-TP5300K, Thermo Fischer Scientific, Waltham, MA, USA) including selected *TP53* coding regions (exons 2 to 11, *NM_000546*) and splice sites (+5 bp). Ion Ampliseq libraries were prepared using 10 ng of genomic DNA. Libraries were qualified using an Agilent 4200 Tape Station System. A total of 200 base-read library templates were prepared with Ion 510 & Ion 520 & Ion 530 kits (Thermo Fischer Scientific) on an automated Ion Chef system (Thermo Fischer Scientific), according to the manufacturer's instructions. Libraries were sequenced on an Ion GeneStudio S5 Plus system (Thermo Fischer Scientific). Torrent Suite version 5.0 software and Ionreporter pipelines (Thermo Fischer Scientific) were used independently to perform the primary analysis.

The prognostic value of all the factors included in the MIPI, MIPIc, and GOELAMS indexes were investigated by univariate analysis: lactate dehydrogenase (LDH) level (N vs. >N), Ki67 ($\leq 30\%$ vs. $>30\%$), ECOG (0-1 vs. 2), B symptoms (No vs. Yes), together with absolute blood lymphocyte count (Lc) (N vs. >5 g/L [$Lc > 5$]), cytological features (common vs. blastoid variant), Alb in g/dL (<3.6 g/dL vs. ≥ 3.6 g/dL) and *TP53* mutational status (*TP53mt* vs. wild-type [*TP53wt*]). For Ki67 analysis, the best cut-off for survival prediction was determined by receiver operating characteristic (ROC) curve analysis (45%; *data not shown*). This cut-off was then applied in further analyses.

Survival functions (PFS and overall survival [OS]) were estimated based on Kaplan-Meier curves. Survival distributions for each parameter were compared using a LogRank test. Cox regression multivariate analysis was performed with parameters significantly associated with PFS or OS according to these univariate analyses (LogRank $P < 0.05$). Statistical analyses were performed with R V4.2.1 software (CRAN).

Results

Cohort characteristics

As described in Gressin *et al.*,¹⁶ 74 patients were recruited (Table 1). Median age was 73 years (range: 69-77). A majority of patients had a high MIPI score (N=58, 69%), 10 (14%) had a blastoid/pleiomorphic cytology, and 34 (59%) presented Ki67 $>30\%$ (Table 1). After six cycles of RiBVD, 56/74 (75.5%) patients were in complete remission (CR).²³

For the update presented here, the median follow-up for

living patients was 115 months (9.6 years) (Figure 1). Thirty-seven patients had died (50%) since the start of the study, with a median OS (mOS) of 111 months (9.3 years). The majority of deaths (21/37, 56%) were lymphoma-related. Other causes of death were: cardiovascular disease (N=4), other cancers (N= 3, Hodgkin lymphoma and adenocarcinoma of the pancreas and bladder), pneumonia (N=1), multifocal leukoencephalopathy (N=1), or unknown cause (N=6). Median PFS (mPFS) was 79 months (6.6 years), with 4 cases remaining in CR at the time of completion of the study. The median duration of response (mDOR) was 95 months (7.9 years). For blood MRD-negative patients after six cycles of RiBVD (87% of the 54 evaluable patients), the mPFS was 106 months (8.8 years).

In total, *TP53* mutational status was analyzed for 54/74 (73%) patients. For 20 patients, lymphoma infiltration in BM and/or blood exceeded 15%, as assessed by flow cytometry. These samples were, therefore, suitable for *TP53* analysis. In addition, tissue samples were available for 45 patients. Both tissue and informative PB/BM samples were available for 9/45 patients. A pathogenic *TP53* mutation (*TP53mt*) was identified in 12 patients (22.2%). For the 9 patients for whom both tissue and PB/BM samples were available, the *TP53* mutational status was fully concordant across both sample types (3 mt and 6 wt). Among *TP53mt* patients, high frequencies of allelic variants were detected in 6/12, suggesting either loss of heterozygosity and/or concomitant *TP53* deletion.

Analysis of the whole cohort and the *TP53* informative cohort revealed no differences in terms of baseline characteristics including MIPI scores, percentage of bulky lesions, extra-nodal involvement, or Ki67 levels (Table 1).

Univariate analysis of TP53 and other baseline prognostic factors at diagnosis

Univariate analysis revealed that patients with *TP53* mutations presented a significantly shorter mPFS (7 months) and mOS (17.5 months) compared to patients with a *TP53wt* status (mPFS 61.5 months and mOS 95 months). *TP53mt* was associated with a worse response to treatment: 3/7 (43%) *TP53mt* MRD informative cases were positive for interim blood MRD as compared to 3/30 (10%) *TP53wt* MRD informative cases. In the final analysis of MRD in blood samples, there were 2/7 (28%) positive cases in the *TP53mt* MRD informative group versus 2/28 (7%) in the *TP53wt* MRD informative group. Finally, disease progression during therapy or within the six months following completion of the treatment schedule was observed in 5/12 (42%) *TP53mt* patients, as compared to 0/42 (0%) *TP53wt* patients.

The following factors were also significantly associated with a shorter PFS according to univariate analysis: lymphocytes >5 g/L, Alb <3.6 g/dL, and Ki67 percentage. For OS, the following variables emerged as statistically significant: ECOG 0-1 versus 2, lymphocytes >5 g/L, Alb <3.6 g/dL, LDH $>N$, Ki67 $>45\%$, and *TP53mt* (*data not shown*).

Table 1. Demographic characteristics of the TP53 informative cohort and of the whole cohort.

	TP53 cohort, N=54 ¹	Total, N=74 ¹	P ²
Age in years	74.5 (69.0-77.0)	73.0 (69.0-77.0)	0.68
Sex			
F	20 (37)	25 (34)	1.7e-12
M	34 (63)	49 (66)	
B symptoms			
No	41 (79)	54 (75)	1.1e-11
Yes	11 (21)	18 (25)	
Histology			
Blastoid/pleiomorphic	9 (18)	10 (14)	2.7e-11
Classic	41 (82)	61 (86)	
MIPI score			
Low/int	11 (20)	14 (31)	1.9e-22
High	43 (80)	58 (69)	
Ki67			
<30 %	16 (37)	24 (41)	4.6e-10
>30 %	27 (63)	34 (59)	
Ki67			
<45 %	30 (70)	43 (74)	5.8e-10
>45 %	13 (30)	15 (26)	
ECOG			
0-1	44 (81)	63 (85)	5.3e-12
2	10 (19)	11 (15)	
LDH rate			
N	34 (63)	44 (61)	1.7e-12
>N	20 (37)	28 (39)	
Albumin			
<3.6 g/dL	38 (76)	56 (78)	2.3e-11
≥3.6 g/dL	12 (24)	15 (22)	
Leukocyte count			
≤5 G/L	38 (70)	56 (76)	2.2e-12
>5 G/L	16 (30)	18 (24)	
Ann Arbor stage			
2	1 (2)	2 (2)	1.0e-22
3	4 (7)	5 (7)	
4	49 (91)	67 (91)	
Extranodal involvement			
No	5 (9)	7 (9)	6.2e-11
Yes	49 (91)	67 (91)	
BM involvement			
No	15 (29)	24 (34)	6.3e-12
Yes	37 (71)	46 (66)	

F: female; M: male; BM: bone marrow; ECOG: Eastern Cooperative Oncology Group; int: intermediate; LDH: lactate dehydrogenase; MIPI: Mantle Cell Lymphoma International Prognostic Index. ¹Median (interquartile range); N (%). ²Wilcoxon rank sum test; Pearson's χ^2 test.

Interestingly, MIPI, MIPIb, and GOELAMS Index were not significantly associated with outcome in this cohort.

Multivariate analyses of prognostic factors at diagnosis

A Cox model was applied to determine PFS, including statistically significant factors identified by univariate analysis (i.e., TP53 status, lymphocytes >5 g/L, LDH >N, Alb <3.6 g/dL and Ki67 >45%) as variables. From this analysis, only TP53mt and Alb <3.6 g/dL emerged as independent prognostic factors for PFS in multivariate analysis. A hazard ratio (HR) of 3.16 (1.3-9.9, $P=0.014$) was found for TP53mt versus TP53wt, and 3.6 (1.39-9.5, $P=0.009$) for Alb <3.6 g/dL versus Alb ≥3.6 g/dL (Figure 2A). When these two prog-

nostic markers were combined, patients with both low Alb and TP53mt (4/50, 8%) had a mPFS of 2.5 months, those with one PF (N=15/50, 30%) had a mPFS of 28 months, and finally those with Alb ≥3.6 g/dL and TP53wt (31/50, 62%) had a mPFS of 93 months (Figure 3A).

For OS, among the statistically significant factors identified by the univariate analysis, three PF appear to independently associate with an unfavorable outcome: TP53mt, ECOG=2 and Alb <3.6 g/dL. The respective HR for these PF are 5.9 (1.77-19.5, $P=0.004$), 5.2 (1.46-18.5, $P=0.011$), and 3.7 (1.31-10.6, $P=0.014$) (Figure 2B). When the three PF were combined, patients with two or all three PF (8/72, 10.5%) had an mOS of 15 months, those with one PF (N=21/72, 28.5%) had an

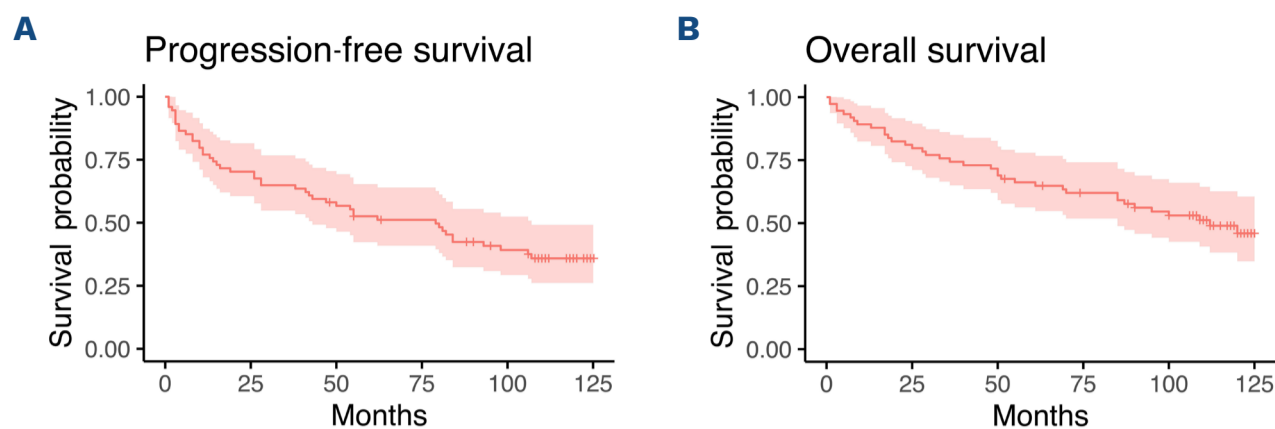


Figure 1. Outcomes for the whole population. Kaplan-Meier estimator of (A) progression-free survival and (B) overall survival for the whole population. Median follow-up was 115 months for surviving patients (N=37, 50%).

mPFS of 63 months, and, for those with no PF (45, 61%), mOS was not reached, and the estimated OS at 10 years was 61% (Figure 3B).

Correlation between TP53 status and p53 immunohistochemistry

Immunohistochemistry-based estimation of p53 expression was available for 9/12 TP53mt and 36/42 TP53wt patients. Mean percentages of positive tumoral cells were 33.6% and 8.1%, respectively ($P=0.004$). The level of p53 expression was above the threshold of 50% in 3/9 TP53mt cases (33.3%) versus 1/36 (2.8%) in the TP53wt group ($P=0.03188$) (Online Supplementary Figure S1).

Discussion

We analyzed the long-term follow-up of the RiBVD phase II trial, involving a population of older adults with MCL. With a median follow-up of 9.6 years, the results confirmed the long-term efficacy of a 6-cycle RiBVD regimen without RM as first-line treatment for older adults with MCL, achieving mPFS and mOS of 5.2 years and 7.5 years, respectively. Our results suggest that this “maintenance-free regimen” is superior than previously published maintenance-free regimens for this age category (median 70-71 years), including R-CHOP, VR-CAP, RBAC500, and BR. With all these other treatment regimens, mPFS was between 22 and 35 months.^{8,19,24-26} In terms of mPFS, RiBVD also compared favorably with more recently published regimens, which always included at least RM. Thus, BR (+/- bortezomib) + RM (+/- lenalidomide)^{15,27} and BR (+/- ibrutinib) + RM (+/- ibrutinib)⁹ achieved complete response rates (CRR) of about 66%, and mPFS between 5.3 and 6.7 years.^{9,15} However, the precise comparison of these regimens is hampered by differences in inclusion criteria (e.g., median patient age 67 years for the ECOG-ACRIN E1411 study,²⁷ and restriction of inclusion to patients with ECOG 0-1 for the SHINE study⁹). We, therefore, propose that the depth of response obtained after six cycles of RiBVD (with a CRR of 75.5% and blood MRD negativity in 87% of patients) could

explain the efficacy observed, even without RM.

In our cohort, none of the multivariate prognostic MIPI, MIPIc or GOELAMS Index²⁸⁻³⁰ scores accurately predicted patient prognosis when treated with the RiBVD regimen. Despite the limited size of our cohort, these results suggest that these prognostic scores should be revisited, especially when dealing with populations of older adults, which is increasingly common. Interestingly, we identified mutations of TP53 and hypoalbuminemia (<3.6 g/dL) as independent unfavorable PF for both PFS and OS in this cohort of older adults with MCL. Based on our findings, TP53 status and albumin level discriminate three populations with a very different prognosis: mPFS of 7.75 years, 28 months, and 2.5 months, respectively, for populations with 0, 1, or 2 PF. Hypoalbuminemia was previously reported as an independent PF only in a few series of older adults with malignant lymphomas, including MCL.³¹⁻³⁴ Here, it is confirmed to be an independent PF in MCL. Hypoalbuminemia is a factor of morbidity usually considered to reflect denutrition and frailty. Our results confirm that intrinsic patient characteristics should be among the considerations to review when choosing treatment strategies in older adults,^{33,34} especially in routine practice, as the real-world population of older adults tends to be more vulnerable and frail than patients included in clinical trials.

TP53 alterations in MCL have been reported in about 10-25% of cases, depending on whether only deletions, mutations, or both are considered.^{4,5,9,14,35,36} Recently, both the World Health Organization (WHO) and the International Consensus Classification of Mature Lymphoid Neoplasms (ICCN) have underlined the interest in molecular assessment of TP53 status in MCL at diagnosis.^{1,37} Nevertheless, whereas the unfavorable impact of TP53 alterations has been clearly demonstrated in young patients,⁴⁻⁷ the prognostic value of TP53 alterations in older adults ineligible for intensive strategies has only been suggested in a few studies.^{38,39} It, therefore, remained to be formally demonstrated. Recently, analysis of survival in the SHINE trial⁹ revealed a lack of benefit of adding ibrutinib to BR, suggesting that ibrutinib-based combinations cannot overcome the unfavorable impact of TP53 mutations in MCL. As yet, few data are

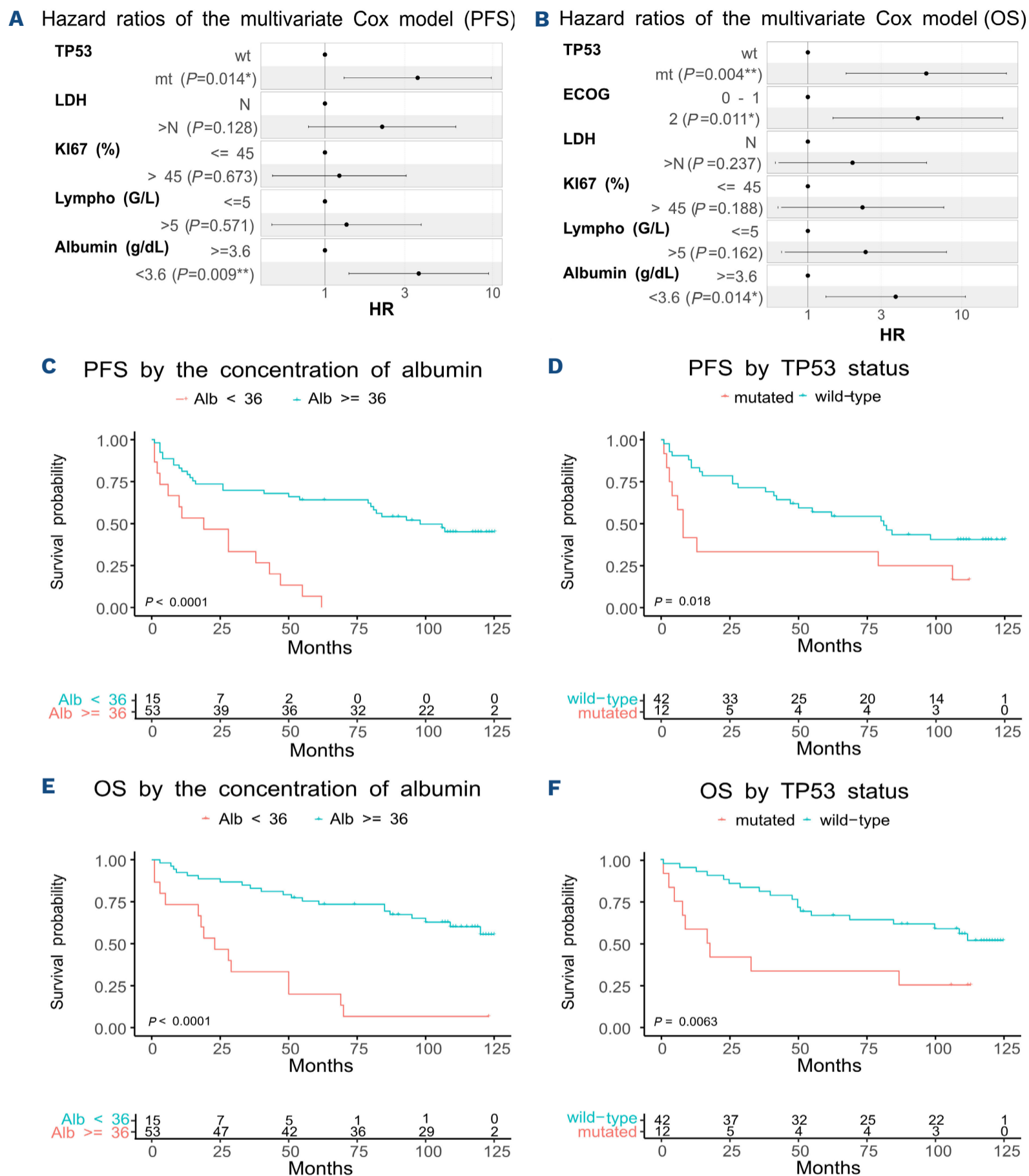


Figure 2. Multivariate analysis identifies albumin level and TP53 status as independent prognostic factors. Hazard ratios determined from multivariate Cox models of (A) progression-free survival (PFS) and (B) overall survival (OS). Only statistically significant factors, as identified by univariate analysis, were tested. Kaplan-Meier estimators for PFS (C-E) and OS (D-F), with patients classed depending on (C and D) albumin level or (E and F) TP53 status. alb: albumin; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; mt: mutated; N: number; wt: wild-type.

available on the efficacy of new targeted agents such as Btk inhibitors, venetoclax, or lenalidomide in patients with TP53 alterations.^{13,20,40,41} Nevertheless, the SHINE results⁹ highlight the need for a systematic assessment of TP53 status in ongoing and future trials to identify any potential benefits of treatments in this high-risk patient population.

Our results in a population of older adults are in line with previous reports; the RiBVD regimen used in this study failed to overcome the unfavorable prognostic impact of TP53 mutations. This finding reinforces the call for routine molecular testing for TP53, even in older adult patients, as proposed by the WHO and the ICCN.

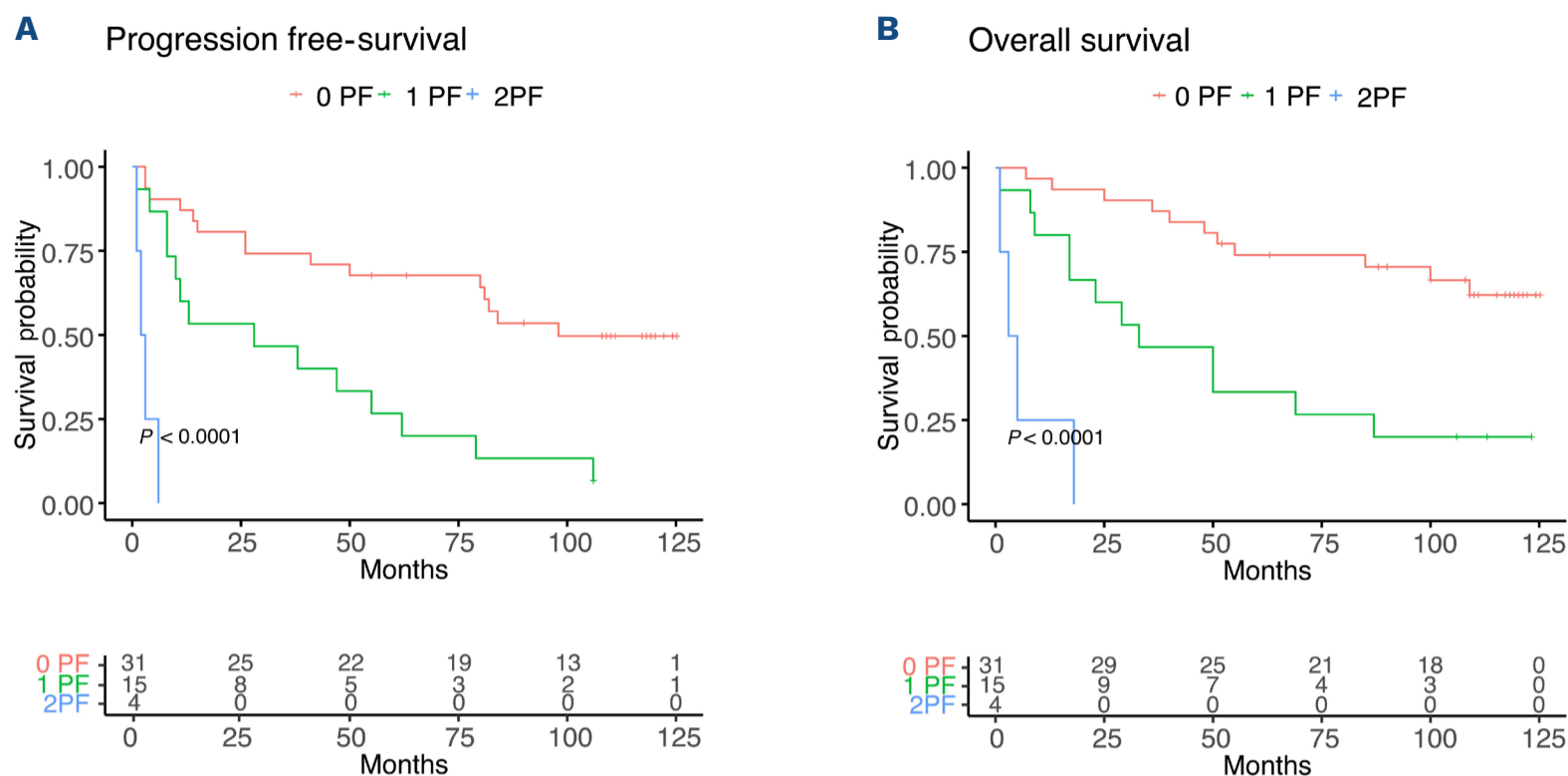


Figure 3. A composite score integrating albumin level and TP53 status is highly predictive for outcomes. Kaplan-Meier estimators for (A) progression-free survival and (B) overall survival. Patients were segregated using a composite score integrating albumin level (<3.6 g/dL or ≥3.6 g/dL) and TP53 status (mutated [mt] vs. wild-type [wt]) as prognostic factors (PF).

Previous studies have shown that high levels of p53 protein are associated with an unfavorable prognosis.²² It has, therefore, been proposed that IHC assessment of p53 expression levels be integrated into prognostic scores.^{42,43} However, despite differences in p53 expression levels between TP53wt and TP53mt samples in our study, IHC-estimated p53 levels do not appear to be a fully reliable surrogate marker for TP53 mutations. Considering the incidence of TP53 mutations and our results, we propose that TP53 status should be systematically assessed and integrated into prognostic indexes in routine practice and future trials, even for older adult patients.

The long-term follow-up presented here confirms the efficacy of the RiBVD regimen with respect to other non-maintenance regimens. The results also suggest that RiBVD compares favorably with more recent regimens integrating RM and iBTK alongside BR induction. Finally, TP53mt and hypoalbuminemia appear to be reliable unfavorable prognostic factors in older adults, and should, therefore, be systematically integrated in early assessments to identify very high-risk MCL patients as a guide to therapeutic de-

cision-making.

Disclosures

No conflicts of interest to disclose.

Contributions

RG was the principal investigator of the clinical trial. MC was the biological investigator of the trial. SC and RG designed the current study, collected data, and wrote the manuscript. SC, AE and AT performed molecular analysis. BB performed histopathological analysis and analyzed IHC results. SC, RG and EM performed statistical analysis. ND, AT, AM ET, AS, RH, CD, SB, SC, AB, LF, JD, MM, JF, FJ, CS, GD, PF, LMF, CC, VD, KB, SA, RG, LV, BJ, NM, MPM, HZ, JF, YA, MA, VD, JPV, LY and SLG actively participated in the clinical trial. All authors reviewed the current manuscript.

Data-sharing statement

Clinical and biological data are available under formal request to the corresponding author.

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