RESEARCH LETTER

blood advances

TO THE EDITOR:

BR or R-CHOP induction with rituximab maintenance in untreated, transplant-ineligible patients with mantle cell lymphoma

Katja Gutmair,[1,*] Diego Villa,[2,*] Nicholas Cunningham,[3] Elisabeth Silkenstedt,[4] Lisa Rimsza,[5] Colleen Ramsower,[5] David W. Scott,[2] Alina S. Gerrie,[2] Hanneke C. Kluin-Nelemans,[6] Martin Dreyling,[4] and Eva Hoster[1]

[1]Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig Maximilian University of Munich, Munich, Germany; [2]Division of Medical Oncology, BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada; [3]Belfast Health and Social Care Trust, Belfast, United Kingdom; [4]Department of Medicine III, University Hospital Ludwig Maximilian University of Munich, Munich, Germany; [5]Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, AZ; and [6]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Rituximab and bendamustine (BR) is a standard first-line regimen in older patients with mantle cell lymphoma (MCL) based on the StiL-1 and BRIGHT trials.[1,2] Maintenance rituximab (MR) is commonly used as part of first-line therapy, based on randomized studies showing an overall survival (OS) benefit after non–bendamustine-based, rituximab-containing regimens.[3,4]

Despite these improvements in first-line therapy, most patients will eventually experience refractory or relapsed (R/R) disease requiring additional therapies. Chimeric antigen receptor (CAR) T-cell therapy is a standard treatment option in patients with R/R MCL and is feasible for many older patients unfit for other intensive therapies, such as autologous stem cell transplantation. Bendamustine alters native T-cell quality and quantity, which is associated with higher rates of CART manufacturing failure.[5,6] Therefore, first-line regimens without bendamustine may be a preferable strategy in fit older patients who may require CAR T-cell therapy.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by MR has been a standard frontline regimen in older patients with MCL for over a decade.[7] There are no data showing that prior R-CHOP exposure is associated with CAR T-cell manufacturing failure in R/R MCL. Although this may be a preferable strategy in older patients potentially heading toward CAR T-cell therapy, physicians may be reluctant to recommend R-CHOP with MR because of improved progression-free survival (PFS) with BR in subgroups of StiL-1 and BRIGHT, indirect comparisons in ENRICH, and retrospective real-world cohorts.[1,2,8-11]

We compared outcomes with R-CHOP and MR in a subgroup of the European MCL Elderly trial (www.ClinicalTrials.gov identifier #NCT00209209)[3] against BR and MR in a consecutively treated, population-based cohort from the Canadian province of British Columbia (BC).[11,12] To maximize comparability between both cohorts, autologous stem cell transplantation–ineligible patients aged ≤85 years with Eastern Cooperative Oncology Group performance status 0 to 2 were included. The same exclusion criteria used for the MCL Elderly trial were applied to the BC Cancer cohort. Additionally, patients from the MCL Elderly cohort were excluded if stage II to IV was not confirmed, if induction treatment was not started, or if they were randomly allocated to rituximab, fludarabine, and cyclophosphamide or interferon as maintenance. In the BC Cancer cohort, only patients who received at least 1 cycle of BR were included. The MCL Elderly trial was approved by the local ethic committees of all participating study centers; all patients provided written informed consent. For the use of BC Cancer database data in this retrospective study, in which obtaining individual patient-informed consent

Submitted 13 November 2024; accepted 11 February 2025; prepublished online on *Blood Advances* First Edition 21 February 2025; final version published online 5 May 2025. https://doi.org/10.1182/bloodadvances.2024015292.

*K.G. and D.V. are joint first authors.

Anonymized clinical data may be shared based on a scientific collaboration upon request sent to the corresponding author, Eva Hoster (ehoster@ibe.med.uni-muenchen.de).

The full-text version of this article contains a data supplement.

Table 1. Baseline characteristics of patients treated with the induction therapy R-CHOP or BR

Characteristic	R-CHOP (n = 141)	BR (n = 98)	*P* value
Age, median (range), y	70 (61-82)	72 (61-83)	.21
Sex, male, n (%)	99 (70)	62 (63)	.27
MIPI			
MIPI, median (range)	6.23 (5.40-8.25)	6.25 (5.34-8.41)	.70
MIPI risk category, n (%)			
Low risk	9 (6)	8 (8)	.76
Intermediate risk	58 (41)	36 (38)	
High risk	74 (52)	52 (54)	
Missing, n (%)	0	2 (2)	
Ki67			
Median (range)	19 (4-80.5)	30 (5-90)	<.001
≥30%, n (%)	18 (26)	49 (55)	<.001
Missing, n (%)	73 (52)	9 (9)	
ECOG performance status, n (%)			
Grade 0-1	131 (93)	71 (72)	<.001
Grade 2	10 (7)	27 (28)	
LDH/upper limit LDH			
Median (range)	0.97 (0.33-11.27)	0.83 (0.50-4.03)	<.001
LDH greater than ULN	60 (43)	29 (30)	.057
Missing, n (%)	0	2 (2)	
WBC, median (range), $\times 10^9$/L	7.900 (3.100-361.750)	7.600 (1.700-177.400)	.77
Ann Arbor stage, n (%)			
II	6 (4)	6 (6)	.81
III	13 (9)	9 (9)	
IV	122 (87)	83 (85)	
Bone marrow involvement, yes, n (%)	113 (80)	70 (71)	.12
Cytology, n (%)			
Classical/small cell	66 (94)	91 (93)	.76
Pleomorphic/blastoid	4 (6)	7 (7)	
Missing	71 (50)	0 (0)	
MCL35			
MCL35 score, median (range)	−194 (−325 to 46)	−146 (−257 to 125)	.056
MCL35 risk category, n (%)			
Low	9 (56)	24 (51)	.40
Intermediate	6 (38)	13 (28)	
High	1 (6)	10 (21)	
Missing values, n (%)	125 (89)	51 (52)	

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell.

would be impossible or impractical, the University of British Columbia/Cancer Research Ethics Board granted a waiver of consent.

In the MCL Elderly subgroup, patients achieving a complete (confirmed or unconfirmed) or partial response after up to 8 cycles of R-CHOP received MR every 2 months until progression or toxicity. In the BC Cancer cohort, patients achieving a complete (confirmed or unconfirmed) or partial response after up to 6 cycles of BR (90 mg/m^2 IV on days 1 and 2 of each cycle) received MR every 3 months until progression, toxicity, or a maximum of 2 years (8 doses). Response assessment and follow-up procedures for both cohorts are described elsewhere.[3,11,12]

The primary end point was PFS, calculated from the start of induction therapy to the date of first progression/relapse or death from any cause, whichever came first. Kaplan-Meier curves and Cox regressions, adjusted for MCL International Prognostic Index (MIPI)[13] alone and additionally for Ki67 (ie, adjusted for combined MIPI) and blastoid/pleomorphic[14] morphology, were calculated.

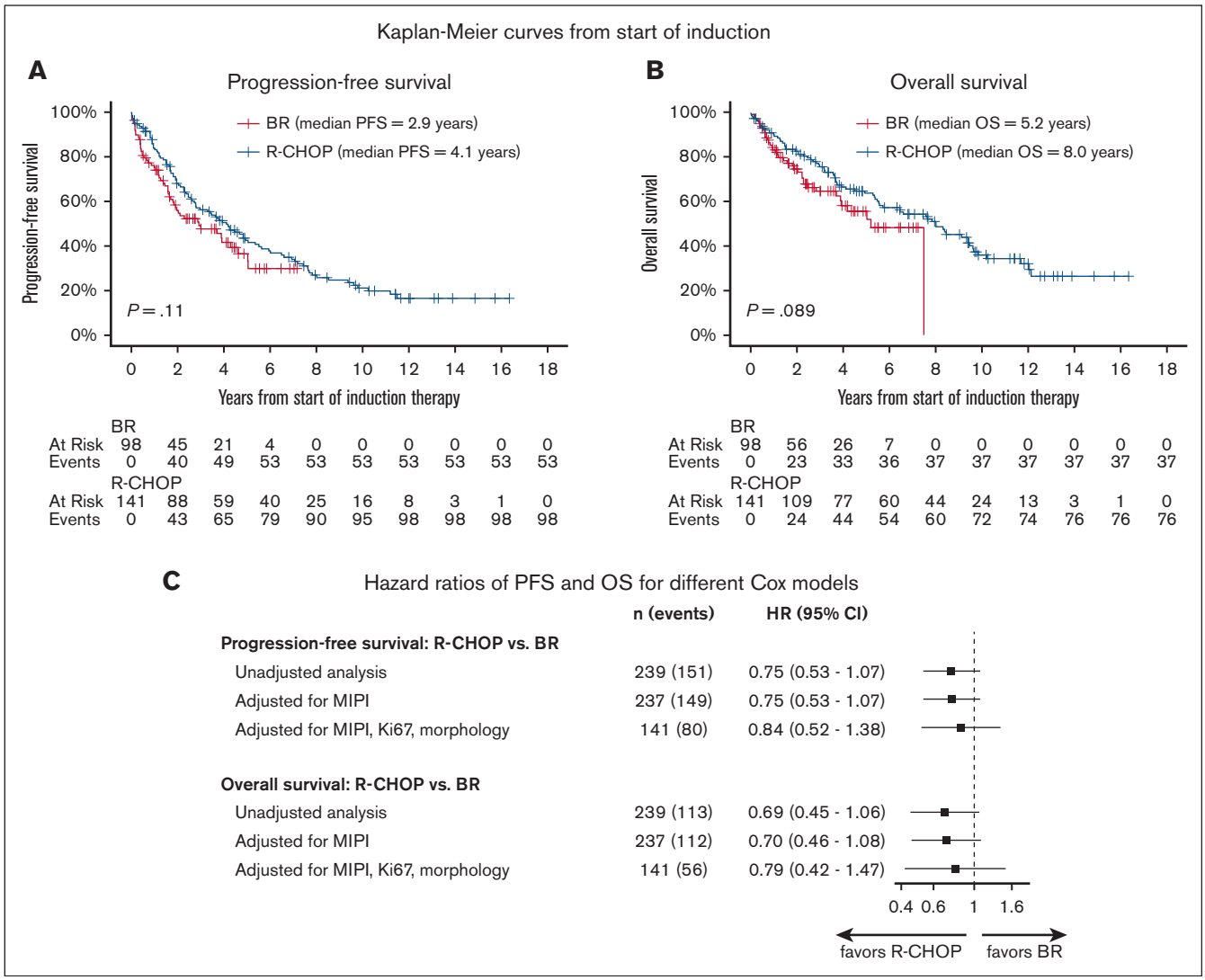

Figure 1. Kaplan-Meier curves and hazard ratios for PFS and OS comparing BR versus R-CHOP. Kaplan-Meier survival curves (A-B) and HRs (C) comparing the treatment regimens R-CHOP + MR vs BR + MR, starting from induction therapy for the primary end point PFS and the secondary end point OS. All patients who started the induction therapy are included. In subplot panel C, both unadjusted and adjusted HRs of the complete case analysis are presented with their corresponding 95% CIs, along with the number of observations and events.

Secondary end points, including OS, and statistical analysis are described in detail in the supplemental Material.

A total of 141 patients treated with R-CHOP from 2004 to 2010 and 98 patients treated with BR from 2013 to 2022 were included in the analysis (supplemental Figure 1). Patients received a median of 8 cycles of R-CHOP (range, 1-8) and 6 cycles of BR (range, 1-6), administered at standard doses.[1,2] Patients treated with BR were slightly older and had a higher proportion of Ki67 ≥30% and a higher percentage of Eastern Cooperative Oncology Group performance status 2, whereas patients treated with R-CHOP had higher lactate dehydrogenase values. The MIPI risk profiles of both cohorts were comparable (Table 1).

The median PFS from the start of induction was 4.1 years (95% confidence interval [CI], 2.8-5.5) for the R-CHOP group and 2.9 years (95% CI, 1.8-5.0; $P = .11$) for the BR group (Figure 1A). The hazard ratios (HRs) for R-CHOP vs BR adjusted for MIPI (HR, 0.75; 95% CI, 0.53-1.07; $P = .11$) or for MIPI, Ki67, and morphology (HR, 0.84; 95% CI, 0.52-1.38; $P = .50$) were not significant. (Figure 1C). After multiple imputations of missing values in MIPI, Ki67, and morphology using multivariate imputation bychained equations, the HR remained similar to the complete case analysis (HR, 0.82; 95% CI, 0.56-1.21; $P = .31$).

After a median follow-up of 9.8 years in the R-CHOP group and 3.7 years in the BR group, there was no significant difference in OS in unadjusted (median OS, R-CHOP, 8.0 years [95% CI, 5.7-9.6]; BR, 5.2 years [95% CI, 3.9 to not reached]; $P = .089$; Figure 1B) or adjusted analyses (HR of R-CHOP vs BR adjusted for MIPI, 0.70; 95% CI, 0.46-1.08; $P = .11$; HR adjusted for MIPI, Ki67, and morphology, 0.79; 95% CI, 0.42-1.47; $P = .45$). After multiple imputations of missing values in these prognostic factors, the HR was 0.78 (95% CI, 0.48-1.27; $P = .31$). Second-line therapy was

started more frequently in the R-CHOP group (52%) than in the BR group (43%), although Bruton tyrosine kinase inhibitors were more frequently used after BR (48% vs <1%), reflecting different treatment eras. There were no significant differences in other secondary outcomes and PFS and OS calculated from the end of induction in the subgroup of patients who responded to induction (supplemental Figure 2D-E).

Although PFS appeared numerically more favorable with R-CHOP than with BR, there were no significant differences in primary or secondary end points after adjustment for prognostic factors. Patients treated with R-CHOP had more favorable prognostic factors and were enrolled in a clinical trial. We addressed these issues by implementing uniform eligibility criteria and adjusting for well-established prognostic factors, but there may remain residual unmeasured imbalances including comorbidities, *TP53* mutations, or other biological factors.[15,16] MCL35 results were not included in the models because they were available in a limited number of patients analyzed in previous studies.[17,18] Furthermore, greater cumulative exposure to MR in the R-CHOP group may have resulted in slightly better outcomes for this group. Conversely, the use of Bruton tyrosine kinase inhibitors for R/R MCL could have improved OS in the BR group.

Our study had sufficient statistical power to rule out relevant PFS differences, similar to a confirmatory superiority trial (80% power to detect a HR of 0.63). However, the power was not sufficient to rule out clinically relevant OS differences, nor can we confirm an equivalence or noninferiority of both treatment regimens. Nevertheless, our results remain clinically relevant because sufficiently powered clinical trials addressing this comparison are currently lacking. Additionally, MR was not (StiL-1) or partially (BRIGHT) administered, and MCL subgroups were small, limiting robust statistical inferences for MCL.[1,2] In ENRICH, the chemoimmunotherapy comparison was not preplanned or powered.[9] In real-world comparisons, BR + MR was associated with improved outcomes compared with R-CHOP + MR, but these were performed in unselected populations without a uniform intent to treat with MR, often without adjustments for imbalances between groups.[10,11]

The decision to use a particular first-line regimen in older patients with MCL incorporates multiple patient, disease, therapy, and health care system factors. Our results reassure clinicians that R-CHOP with MR is an appropriate alternative to BR with MR in older patients expected to eventually require CAR T-cell therapy for R/R MCL.

Contribution: K.G. analyzed the data, prepared the figures, wrote the manuscript, and interpreted the data; D.V. designed the research, acquired data, and wrote the manuscript; N.C. acquired data and reviewed the manuscript; E.S. reviewed the manuscript; L.R., C.R., D.W.S., and A.S.G. acquired data and reviewed the manuscript; H.C.K.-N. was the principal investigator of the MCL Elderly trial and reviewed the manuscript; M.D. and D.V. designed the research, acquired data, and reviewed the manuscript; and E.H. designed the research, provided supervision in statistical analysis, acquired data, and reviewed the manuscript.

Conflict-of-interest disclosure: D.V. reports research funding (to the institution) from Roche and AstraZeneca, and advisory board fees and honoraria from Roche, AstraZeneca, AbbVie, BeiGene, Janssen, Merck, Novartis, Kite/Gilead, and Bristol Myers Squibb/Celgene. D.W.S. reports consultancy for AbbVie, AstraZeneca, Genmab, Roche, and Veracyte, and research funding from Roche/Genentech. The remaining authors declare no competing financial interests.

The current affiliation for L.R. and C.R. is Department of Pathology and Laboratory Medicine, University of Arizona, Tucson, AZ.

ORCID profiles: K.G., 0009-0002-3948-6186; D.V., 0000-0002-4625-3009; E.S., 0000-0003-2676-0860; C.R., 0000-0002-4991-7712; D.W.S., 0000-0002-0435-5947; A.S.G., 0000-0003-4727-1425; H.C.K.-N., 0000-0003-2617-9427; M.D., 0000-0002-0358-5249; E.H., 0000-0002-0749-1389.

Correspondence: Eva Hoster, Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig Maximilian University of Munich, Marchioninistr 15, 81377 Munich, Germany; email: ehoster@ibe.med.uni-muenchen.de.

References

1. Flinn IW, van der Jagt R, Kahl B, et al. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: results of the BRIGHT 5-year follow-up study. *J Clin Oncol*. 2019;37(12):984-991.
2. Rummel MJ, Maschmeyer G, Ganser A, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: nine-year updated results from the StiL NHL1 study. *J Clin Oncol*. 2017;35(suppl 15):7501.
3. Kluin-Nelemans HC, Hoster E, Hermine O, 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(3):248-256.
4. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med*. 2017;377(13):1250-1260.
5. Wang Y, Jain P, Locke FL, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in standard-of-care practice: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2023;41(14):2594-2606.
6. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. *J Clin Oncol*. 2023;41(3):555-567.
7. Kluin-Nelemans JC, Doorduijn JK. What is the optimal initial management of the older MCL patient? *Best Pract Res Clin Haematol*. 2018;31(1):99-104.
8. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
9. Lewis DJ, Jerkeman M, Sorrell L, 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(suppl 1):235.

10. Martin P, Cohen JB, Wang M, 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*. 2023;41(3):541-554.

11. Villa D, Sehn LH, Savage KJ, et al. Bendamustine and rituximab as induction therapy in both transplant-eligible and -ineligible patients with mantle cell lymphoma. *Blood Adv*. 2020;4(15): 3486-3494.

12. Villa D, Hoster E, Hermine O, et al. Bendamustine or high-dose cytarabine-based induction with rituximab in transplant-eligible mantle cell lymphoma. *Blood Adv*. 2022;6(18):5285-5294.

13. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008; 111(2):558-565.

14. Hoster E, Rosenwald A, Berger F, 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(12):1386-1394.

15. Scheubeck G, Jiang L, Hermine O, et al. Clinical outcome of mantle cell lymphoma patients with high-risk disease (high-risk MIPI-c or high p53 expression). *Leukemia*. 2023;37(9):1887-1894.

16. Eskelund CW, Dahl C, Hansen JW, et al. *TP53* mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood*. 2017;130(17):1903-1910.

17. Rauert-Wunderlich H, Mottok A, Scott DW, et al. Validation of the MCL35 gene expression proliferation assay in randomized trials of the European Mantle Cell Lymphoma Network. *Br J Haematol*. 2019; 184(4):616-624.

18. Ramsower CA, Rosenthal A, Robetorye RS, et al. Evaluation of clinical parameters and biomarkers in older, untreated mantle cell lymphoma patients receiving bendamustine-rituximab. *Br J Haematol*. 2024; 204(1):160-170.