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Predictive Value of Minimal Residual Disease for Efficacy of Rituximab Maintenance in Mantle Cell Lymphoma: Results From the European Mantle Cell Lymphoma Elderly Trial

Eva Hoster, PhD[1,2]; Marie-Hélène Delfau-Larue, PhD[3]; Elizabeth Macintyre, MD, PhD[4]; Linmiao Jiang, MSc[1]; Stephan Stilgenbauer, MD, PhD[5]; Ursula Vehling-Kaiser, MD[6]; Gilles Salles, MD, PhD[7,8]; Catherine Thieblemont, MD, PhD[9]; Hervé Tilly, MD, PhD[10]; Stefan Wirths, MD[11]; Pierre Feugier, MD, PhD[12]; Kai Hübel, MD, PhD[13]; Christian Schmidt, MD[2]; Vincent Ribrag, MD, PhD[14]; Johanna C. Kluin-Nelemans, MD, PhD[15]; Martin Dreyling, MD, PhD[2]; and Christiane Pott, MD, PhD[16]; on behalf of the European MCL MRD Working Group and the European MCL Network

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ABSTRACT

PURPOSE The outcome of older patients with mantle cell lymphoma (MCL) has improved by the introduction of immunochemotherapy, followed by rituximab (R)-maintenance. Assessment of minimal residual disease (MRD) represents a promising tool for individualized treatment decisions and was a prospectively planned part of the European MCL Elderly trial. We investigated how MRD status influenced the efficacy of R-maintenance and how MRD can enable tailored consolidation strategies.

PATIENTS AND METHODS Previously untreated patients with MCL age 60 years or older have been randomly assigned to R versus interferon-alpha maintenance after response to rituximab, fludarabine, cyclophosphamide (R-FC) versus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). MRD monitoring was performed by real-time quantitative polymerase chain reaction (qPCR) following EuroMRD guidelines.

RESULTS A qPCR assay with a median sensitivity of 1×10^{-5} could be generated in 80% of 288 patients in an international, multicenter, multilaboratory setting. More extensive tumor dissemination facilitated the identification of a molecular marker. The efficacy of R-maintenance in clinical remission was confirmed for MRD-negative patients at the end of induction in terms of progression-free survival (PFS; hazard ratio [HR], 0.38 [95% CI, 0.21 to 0.63]) and overall survival (OS; HR, 0.37 [95% CI, 0.20 to 0.68]), particularly in R-CHOP–treated patients (PFS-HR, 0.23 [95% CI, 0.10 to 0.52]; OS-HR, 0.19 [95% CI, 0.07 to 0.52]). R-maintenance appeared less effective in MRD-positive patients (PFS-HR, 0.51 [95% CI, 0.26 to 1.02]) overall and after R-CHOP induction (PFS-HR, 0.59 [95% CI, 0.28 to 1.26]). R-FC achieved more frequent and faster MRD clearance compared with R-CHOP. MRD positivity in clinical remission after induction was associated with a short median time to clinical progression of approximately 1-1.7 years.

CONCLUSION The results confirm the strong efficacy of R-maintenance in patients who are MRD-negative after induction. Treatment de-escalation for MRD-negative patients is discouraged by our results. More effective consolidation strategies should be explored in MRD-positive patients to improve their long-term prognosis.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Mantle cell lymphoma (MCL) is a relatively uncommon and incurable hematological malignancy.[1] With the introduction of immunochemotherapy,[2] high-dose treatment followed by autologous stem-cell transplantation (ASCT),[3,4] high-dose cytarabine-containing induction,[5] and rituximab (R) maintenance[6,7] (European Society for Medical Oncology guideline,[1] National Comprehensive Cancer Network guideline version 2.2023), the clinical course of advanced-stage MCL has substantially improved during the past two decades.

The variability of outcome in advanced-stage MCL can be partly explained by clinical variables (age, performance status, lactate dehydrogenase [LDH], and WBC count, integrated in the MCL International Prognostic Index [MIPI])[8,9] and the

CONTEXT

Key Objectives

In the European Mantle Cell Lymphoma (MCL) Elderly trial, we investigated the efficacy of rituximab (R) maintenance in MCL depending on the presence or absence of minimal residual disease (MRD) after first-line induction with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone or rituximab, fludarabine, cyclophosphamide Furthermore, we searched for trigger points for novel MRD-guided treatment strategies.

Knowledge Generated

R-maintenance was highly effective in MRD-negative patients at the end of induction by prolonging progression-free and overall survival. Treatment de-escalation in MRD-negative patients is strongly discouraged. MRD positivity after start of R-maintenance was associated with short time to progression and represents an important trigger for treatment intensification to be developed in future studies.

Relevance *(J.W. Friedberg)*

These long-term results further demonstrate the value of MRD assessment in MCL, and show that de-escalation strategies for patients achieving undetectable MRD are not recommended.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

Ki-67 index of proliferation.[10] Currently, treatment decisions are mainly guided by clinical characteristics such as leukemic, non-nodal presentation, Ann Arbor stage, and age.[1] The detection of minimal residual disease (MRD) allows a highly sensitive longitudinal monitoring of tumor load and residual disease during and after treatment in different mature B-cell malignancies such as MCL,[11] chronic lymphocytic leukemia,[12] and follicular lymphoma (FL).[13] Importantly, MRD assessment has been standardized[14] and is nowadays established as a routine tool to guide treatment in ALL.[15]

The European MCL Elderly trial (ClinicalTrials.gov identifier: NCT00209209) was an international, double-randomized phase III trial that established R-maintenance in older patients with MCL responding to first-line rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) on the basis of prolonged progression-free survival (PFS) and overall survival (OS).[6,7] Furthermore, compared with R-CHOP, induction treatment with rituximab, fludarabine, cyclophosphamide (R-FC) was not superior in terms of response rates and failure-free survival and was inferior in terms of OS, mainly because of increased early and late toxicity.[6,7]

Within the European MCL Network, MRD monitoring has been established as a standard correlative program for clinical trials. For MCL Elderly, our primary aim was to investigate whether and how the MRD status at the end of induction (EOI) influenced the efficacy of R-maintenance and particularly to answer the question whether treatment de-escalation in MRD-negative patients should be encouraged. Secondary aims were to confirm the feasibility of MRD assessment for prognostic analyses in a multicenter, multinational trial setting, to evaluate the use of MRD status as a dynamic indicator for induction treatment efficacy, and to establish optimal MRD time points for treatment modification.

PATIENTS AND METHODS

Patients

From January 2004 to October 2010, 560 previously untreated patients with Ann Arbor stage II-IV MCL, age 60 years or older and not suitable for ASCT were recruited to MCL Elderly. The trial was performed in eight European countries, with the support of four study groups (GELA, HOVON, NLG, and GLSG). Patients gave written informed consent to trial participation including collection and analysis of MRD samples. The trial adhered to the Declaration of Helsinki and was approved by ethics committees of the participating centers.

Random Assignment, Treatment, and Outcomes

Patients were first randomly assigned between induction with six 28-day cycles R-FC and eight 21-day cycles R-CHOP. Patients responding to induction with complete remission (CR; unconfirmed CR [CRu]) or partial remission (PR)[16] were subsequently offered random assignment between maintenance with R or interferon-alpha (IFN) until progression, stratified for induction treatment and EOI response. Of note, the median duration of IFN-maintenance was only 10 months versus 2.2 years for R-maintenance.[7] Clinical outcomes were response duration (RD) from EOI to progression or death (the trial's primary maintenance efficacy outcome) and OS to assess the efficacy of maintenance and CR at EOI and time to progression (TTP) from various landmark time points (censoring death in clinical remission) to assess the prognostic value of MRD.

MRD Assessment

MRD samples from peripheral blood (PB) and bone marrow (BM) were collected by central diagnostic laboratories in France, Denmark, the Netherlands, and Germany. For administrational reasons, MRD analysis was restricted to patients recruited in France or Germany. MRD sampling time points were at baseline, midterm induction (MI, optional, after three cycles R-FC, or four cycles R-CHOP), EOI, and every 2 (BM, 6) months during maintenance or follow-up until progression. The results of MRD assessment were not incorporated into response evaluation and did not influence patient management.

The details on MRD marker generation, quantitative polymerase chain reaction (qPCR) assay establishment, and MRD analysis have been reported previously.[17] In summary, DNA from diagnostic PB or PB mononuclear cells and BM was extracted and analyzed by t(11;14) PCR and *IGH* multiplex PCR to identify the clonal rearrangement.[18,19] Sequencing of clonal rearrangements was performed by using the BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Darmstadt, Germany). For subsequent MRD analysis, at least one marker (either t(11;14) or *IGH*) identified in either PB or BM was sufficient. Marker screening was only performed if a follow-up MRD sample was available. Quantitative PCR with allele-specific oligonucleotides was performed as previously described, establishing assay sensitivity and quantitative range (QR).[14] Assays were established aiming to reach a sensitivity of 10^{-5}, tested by analyzing 10-fold serial dilutions from diagnostic samples in polyclonal DNA derived from pooled mononuclear cells of healthy donors. The degree of lymphoma involvement of the diagnostic sample was determined by four-color flow cytometry[20] or droplet digital PCR[21] and subsequently used to establish standard dilution series of the diagnostic specimen for real-time qPCR for each individual patient. Four-color flow cytometry of the diagnostic sample was also used to

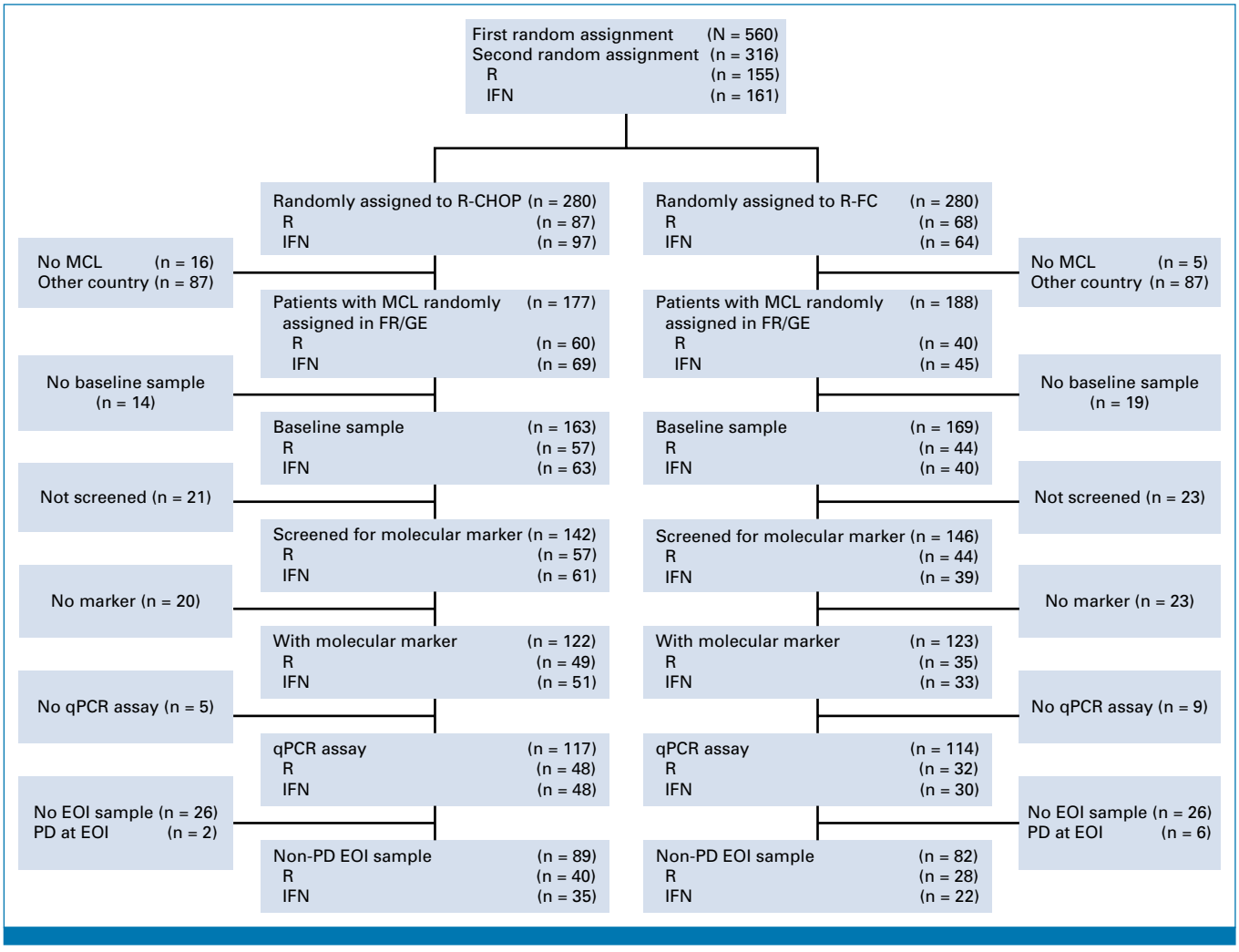

FIG 1. CONSORT diagram. EOI, end of induction; FR, France; FU, follow-up; GE, Germany; IFN, interferon-alpha; MCL, mantle cell lymphoma; PD, progressive disease; qPCR, real-time quantitative polymerase chain reaction; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FC, rituximab, fludarabine, cyclophosphamide.

assure the specificity of the clonal rearrangement for MRD marker detection. For MRD assessment in follow-up samples, the results of qPCR were evaluated according to EuroMRD criteria.[14] Positive nonquantifiable MRD samples were classified as positive below the QR (BLQ) and considered MRD positive according to EuroMRD criteria.[14] The involved MRD laboratories participated in 6 monthly quality control rounds of the EuroMRD network.

Statistical Methods

Patients were excluded if no qPCR assay had been established, assay sensitivity was $>1.2 \times 10^{-4}$, or no MRD sample was available at the respective sampling time point. Sampling bias was investigated by comparing characteristics and outcome of patients selected versus excluded based on different factors. MRD status was classified either binary (positive, including positive BLQ, *v* negative) or in three groups (quantifiably positive, positive BLQ, or negative). At MI and EOI, MRD status was pooled from PB and BM by classifying a patient only as MRD negative if all available PB and BM samples were MRD negative. MRD samples immediately before and thus directly reflecting clinical progression were excluded (PD at MI or EOI, respectively, up to 60 days before clinical progression in follow-up), to capture prognostic effects of MRD and considering the 3-month follow-up staging interval. Kaplan-Meier estimates and log-rank tests were applied to analyze time-to-event variables in groups defined by maintenance or MRD status. The predictive value of MRD status at EOI for efficacy of maintenance was investigated by subgroup analyses and by Cox regression on RD and OS including the interaction term of MRD status and maintenance group. To investigate the prognostic value of MRD status for TTP, Cox models were applied adjusting for MIPI score, clinical remission (CR/CRu/PR), and maintenance (R/no R).

RESULTS

MRD Marker Screening and Patient Characteristics

Among 365 patients with confirmed MCL randomly assigned in France or Germany, 332 (91%) had a baseline sample available and 288 were screened for a molecular marker

TABLE 1. Baseline Characteristics According to Success of qPCR Assay Establishment

Variable	Randomly Assigned	Screened for Marker	Molecular Marker	qPCR Assay	*P*[a]
No. of patients	365	288	245	231	
Age, years, median (range)	70 (60-87)	70 (60-87)	71 (60-87)	71 (60-87)	.57
Male sex, No. (%)	260 (71)	203 (70)	175 (71)	164 (71)	>.99
Stage I, No. (%)	1 (0)	1 (0)	1 (0)	1 (0)	.0003
Stage II, No. (%)	22 (6)	18 (6)	7 (3)	6 (3)	
Stage III, No. (%)	48 (13)	38 (13)	28 (11)	25 (11)	
Stage IV, No. (%)	294 (81)	231 (80)	209 (85)	199 (86)	
B-symptoms, No. (%)	130 (36)	98 (34)	87 (36)	78 (34)	.36
ECOG PS 0, No. (%)	168 (46)	139 (48)	118 (48)	112 (48)	.40
ECOG PS 1, No. (%)	167 (46)	129 (45)	110 (45)	102 (44)	
ECOG PS 2, No. (%)	30 (8)	20 (7)	17 (7)	17 (7)	
BM involved, No. (%)	267 (73)	208 (72)	192 (78)	183 (79)	.0009
LDH elevated, No. (%)	158 (43)	111 (39)	99 (40)	94 (41)	.19
LDH/ULN, median (range)	0.95 (0.29-11.3)	0.91 (0.29-11.3)	0.93 (0.29-3.83)	0.94 (0.29-3.83)	.99
WBC, G/L, median (range)	7.4 (1.1-396)	7.3 (1.1-396)	7.3 (1.1-396)	7.5 (1.1-396)	.48
MIPI score, median (range)	6.17 (4.97-8.52)	6.14 (4.97-8.52)	6.17 (4.97-8.25)	6.17 (4.97-8.25)	.96
MIPI low risk, No. (%)	33 (9)	29 (10)	20 (8)	16 (7)	.077
MIPI intermediate risk, No. (%)	158 (43)	134 (47)	114 (47)	108 (47)	
MIPI high risk, No. (%)	174 (48)	125 (43)	111 (45)	107 (46)	
Ki-67 index, %, median (range)	20 (2-91, n = 240)	19 (3-91, n = 196)	19 (3-91, n = 166)	19 (3-91, n = 155)	.039
Ki-67 index ≥30%, No. (%)	79 (33, n = 240)	59 (30, n = 196)	50 (30, n = 166)	48 (31, n = 155)	.39
Blastoid MCL, No. (%)	32 (12, n = 257)	25 (12, n = 204)	20 (12, n = 173)	18 (11, n = 162)	.44
R-FC group, No. (%)	188 (52)	146 (51)	123 (50)	114 (49)	.33
CR/CRu/PR at EOI, No. (%)	291 (84, n = 348)	254 (90, n = 282)	217 (91, n = 239)	204 (91, n = 225)	<.0001

Abbreviations: BM, bone marrow; CR, complete remission; CRu, unconfirmed CR; ECOG PS, ECOG performance status; EOI, end of induction; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; PR, partial remission; qPCR, real-time quantitative polymerase chain reaction; R-FC, rituximab, fludarabine, cyclophosphamide; ULN, upper limit of normal.

[a]*P* value for the comparison of 231 patients with qPCR assay compared with 134 randomly assigned patients without qPCR assay (Fisher exact test for categorical or Mann-Whitney-U-test for numerical variables).

(Fig 1; Data Supplement, Table S1 [online only]). Of the latter, 85% (n = 245) had a molecular marker, and in 80% (n = 231), a qPCR assay fulfilling standardized criteria could be established. The median assay sensitivity was 1.0×10^{-5} (IQR, 1.0×10^{-5}-3.0×10^{-5}; range, 4.0×10^{-6}-1.2×10^{-4}), and the median QR was 1.0×10^{-4} (range, 1.0×10^{-5}-7.8×10^{-3}).

Patients screened for a molecular marker had a more favorable risk profile than patients not screened (Table 1; Data Supplement, Table S1B), and patients with a clonal marker had more frequently stage IV and BM involvement and higher LDH (Data Supplement, Table S1C). Overall, patients monitored for MRD had no substantially different long-term outcome compared with those not monitored (Data Supplement, Fig S1).

MRD Response at MI and EOI

MRD samples at MI were available for 166 (72%) of 231 non-PD patients with qPCR assay. At MI, MRD negativity was more frequent after R-FC than after R-CHOP in pooled PB/BM (63% of 82 *v* 26% of 84; $P < .0001$), PB (72% of 78 *v* 33% of 78; $P < .0001$), and BM (60% of 43 *v* 29% of 51; $P = .0034$; Fig 2). Consistently, quantifiable MRD positivity was less frequent after R-FC (PB, 14%, BM, 16%) than after R-CHOP (PB, 28%; BM, 41%). Similar results were obtained when defining MI strictly as after three cycles of R-FC and four cycles of R-CHOP, not allowing for deviations by one cycle (not shown).

At EOI, MRD samples were available for 171 (79%) of 217 non-PD patients. Similar to MI, MRD negativity was more frequent after R-FC versus R-CHOP in pooled PB/BM (80% of 82 *v* 53% of 89; $P = .0002$), PB (83% of 80 *v* 64% of 87; $P = .0092$), and BM (82% of 45 *v* 52% of 58 patients; $P = .0017$; Fig 2). Quantifiable MRD positivity was seen in 9% (PB) and 7% (BM) after R-FC as compared with 7% (PB) and 28% (BM) after R-CHOP, suggesting that the difference in MRD negativity rates between treatment groups at EOI was mainly driven by low-level MRD positivity in PB and quantifiable positivity in BM. Thus, the chemotherapy backbones showed different effects on tumor cell clearance in different MRD compartments. The Data Supplement contains details on MRD status considering clinical response, kinetics, and compartments.

Predictive Value of MRD Status for the Efficacy of R-Maintenance

Of the 222 patients with MCL randomly assigned for maintenance in France or Germany, 158 had a qPCR assay established, of whom 125 (79%) were evaluable for MRD status at EOI (Fig 1). The prolongation of RD by R-maintenance was clearly confirmed in patients achieving MRD negativity at EOI in pooled PB/BM (hazard ratio [HR], 0.38 [95% CI, 0.21 to 0.63]; n = 84), in PB only (HR, 0.38 [95% CI, 0.23 to 0.63]; n = 90), and in BM only (HR, 0.28 [95% CI, 0.14 to 0.57]; n = 53; Fig 3A; Data Supplement, Table S2 and Figs S2A and S3A). Slightly smaller effects were observed in MRD-positive patients in pooled PB/BM (HR, 0.51 [95% CI, 0.26 to 1.03]; n = 41), PB (HR, 0.40 [95% CI, 0.18 to 0.87]; n = 32), and BM (HR, 0.64 [95% CI, 0.28 to 1.48]; n = 26; Fig 3B; Data Supplement, Figs S2B and S3B). The prolongation of OS by R-maintenance was also confirmed for MRD-negative patients (HR, 0.37 [95% CI,

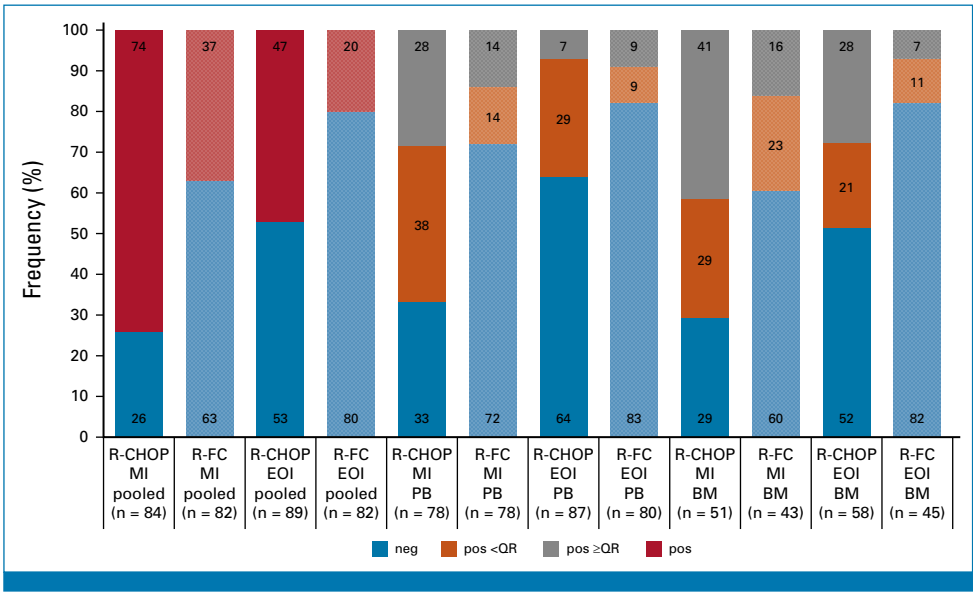

FIG 2. MRD status at MI and EOI stratified by treatment group and MRD compartment. Darker/lighter bars show MRD status in R-CHOP/R-FC groups. BM, bone marrow; EOI, end of induction; MI, midterm induction; MRD, minimal residual disease; neg, MRD-negative; PB, peripheral blood; pooled, pooled PB/BM; pos, MRD-positive; QR, quantitative range; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FC, rituximab, fludarabine, cyclophosphamide.

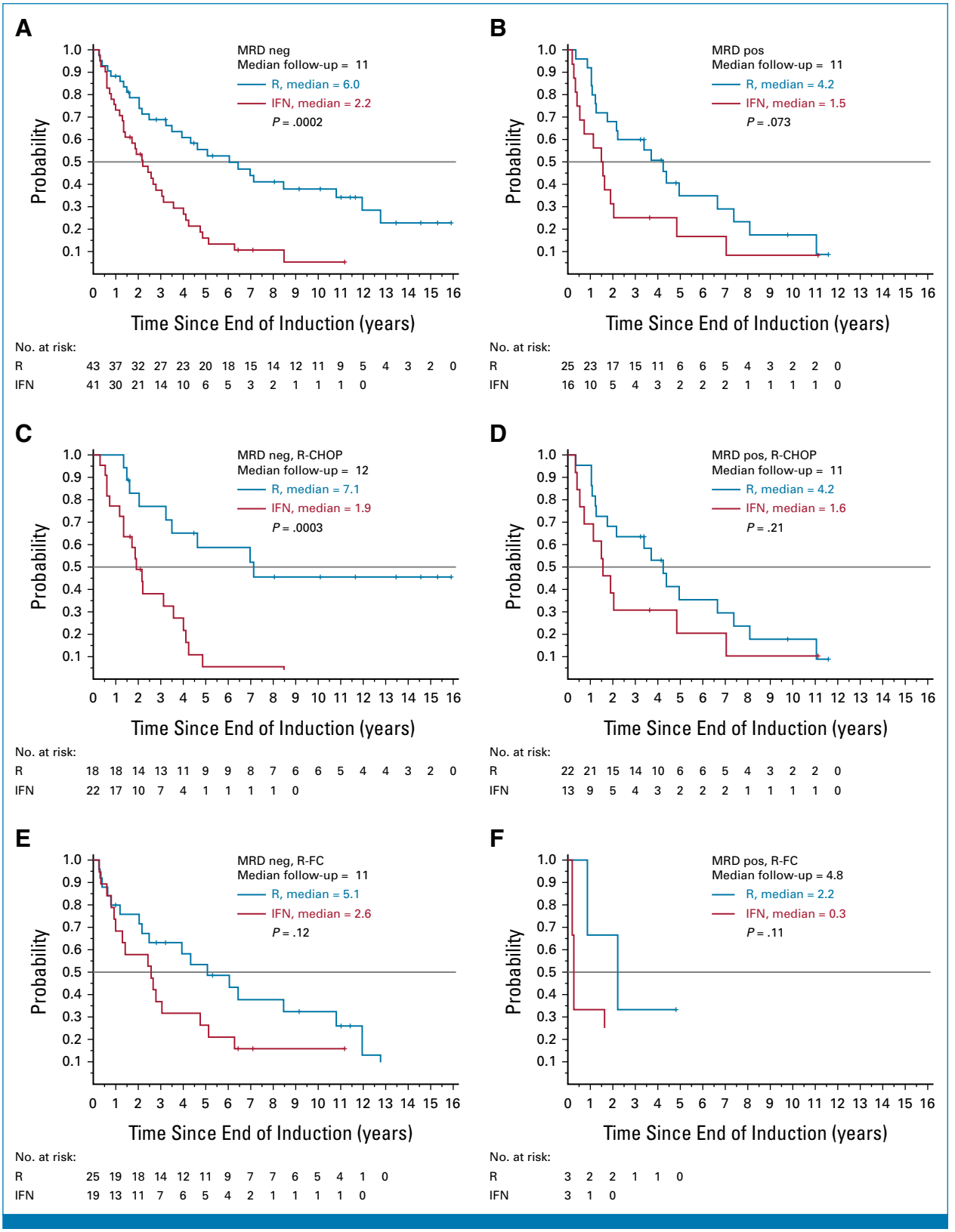

FIG 3. Efficacy of R-maintenance on RD stratified by MRD status at the end of induction pooled from peripheral blood and bone marrow (A and B) in all patients, (C and D) in patients treated with R-CHOP, and (E and F) in patients treated with R-FC. (A) RD for MRD-negative patients, (B) RD for MRD-positive patients, (C) RD for MRD-negative patients treated with R-CHOP, (D) RD for MRD-positive patients treated with R-CHOP, (E) RD for MRD-negative patients treated with R-FC, (F) RD for MRD-positive patients treated with R-FC. IFN, interferon-alpha; MRD, minimal residual disease; neg, negative; pos, positive (including both MRD-positive below quantifiable range and positive quantifiable); R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RD, response duration; R-FC, rituximab, fludarabine, cyclophosphamide.

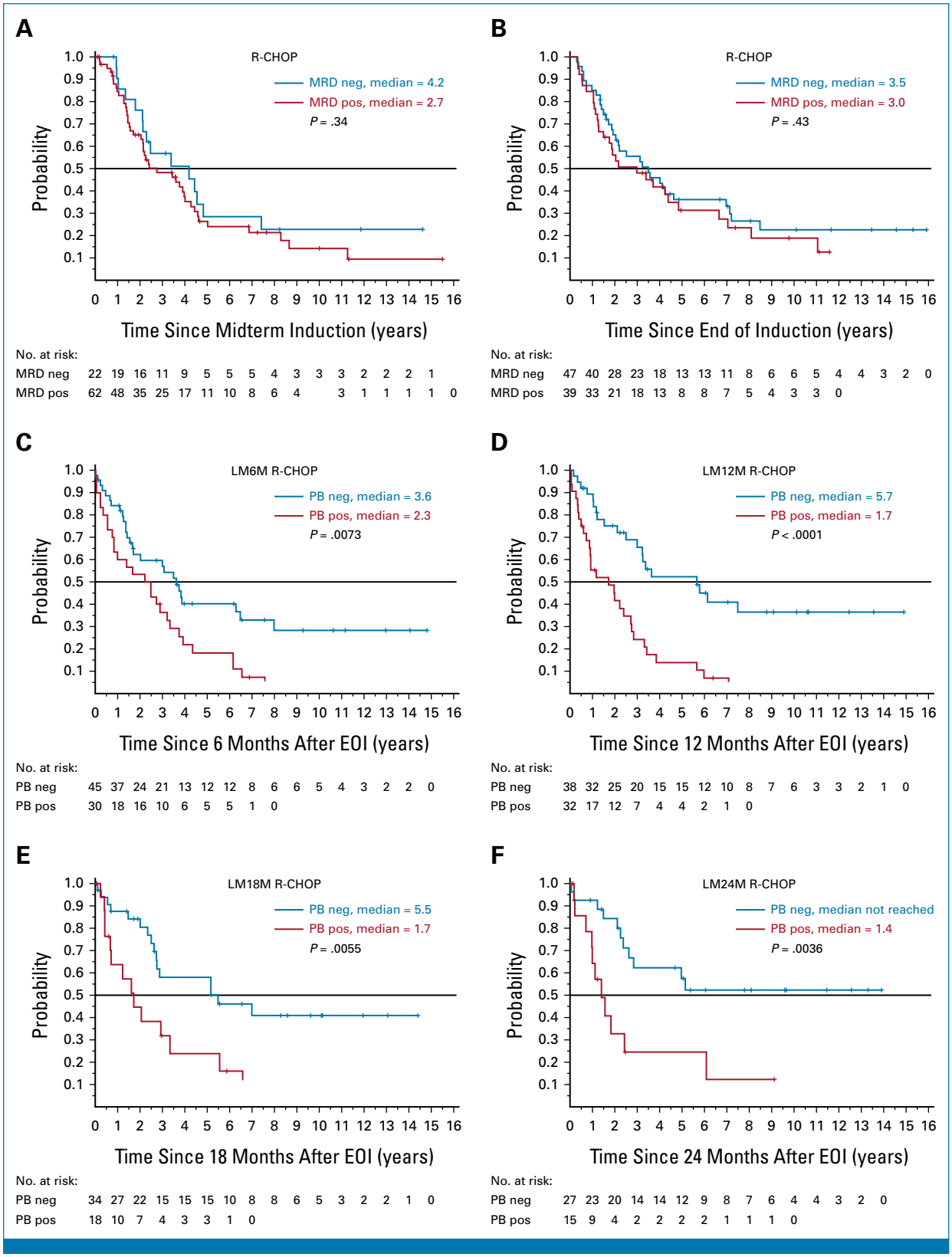

FIG 4. Prognostic value of MRD status for TTP from (A) MI, (B) EOI, and (C-F) from landmark time points 6/12/18/24 months after EOI in R-CHOP group among patients progression-free up to the landmark. (A) TTP according to MRD status at MI pooled from PB and BM, HR (95% CI) adjusted for MIPI score: 1.31 (0.72 to 2.35); (B) time to progression according to MRD status at EOI pooled from PB and BM, HR (95% CI) adjusted for MIPI score, clinical remission, and maintenance: 0.94 (0.53 to 1.69); (C-F) time to progression according to MRD status in PB before the LM point (C) 6/(D) 12/(E) 18/(F) 24 months from EOI; HRs (95% CI) adjusted for MIPI score, clinical remission and maintenance (C) 2.03 (1.14 to 3.62), (D) 2.96 (1.57 to 5.58), (E) 2.54 (1.16 to 5.57), and (continued on following page)

FIG 4. (Continued). (F) 2.35 (0.89 to 6.19). To assess prognostic effects of MRD status on time to clinical progression, death in clinical remission was censored. BM, bone marrow; EOI, end of induction; HR, hazard ratio; LM, landmark; M, month from EOI; MI, midterm induction; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, minimal residual disease; neg, negative; PB, peripheral blood; pos, positive (including both, MRD-positive below quantifiable range and positive quantifiable); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; TTP, time to progression.

0.20 to 0.68]; pooled PB/BM; Data Supplement, Table S2 and Fig S4A), whereas in MRD-positive patients, the OS effects appeared reduced (HR, 0.80 [95% CI, 0.34 to 1.84]; Data Supplement, Table S2 and Fig S4B).

Especially after R-CHOP, the efficacy of R-maintenance on RD was strong in MRD-negative patients at EOI in pooled PB/BM (HR, 0.23 [95% CI, 0.10 to 0.52]; n = 40; Fig 3C), PB (HR, 0.30 [95% CI, 0.14 to 0.61]; n = 47; Data Supplement, Fig S2C), and BM (HR, 0.22 [95% CI, 0.08 to 0.65]; n = 26; Data Supplement, Fig S3C). Similarly, after R-CHOP, the benefit from R-maintenance appeared less prominent in MRD-positive patients in pooled PB/BM (HR, 0.59 [95% CI, 0.28] to 1.27]; n = 35; Fig 3D), PB (HR, 0.45 [95% CI, 0.19 to 1.07]; n = 27; Data Supplement, Fig S2D), and BM (HR, 0.82 [95% CI, 0.33 to 2.03]; n = 23; Data Supplement, Fig S3D). A prolongation of OS by R-maintenance was also clearly confirmed for MRD-negative patients after R-CHOP (HR, 0.19 [95% CI, 0.07 to 0.52]; pooled PB/BM; Data Supplement, Table S2 and Fig S4C), whereas in MRD-positive patients, the OS efficacy was reduced (HR, 0.91 [95% CI, 0.36 to 2.3]; Data Supplement, Table S2 and Fig S4D).

After R-FC, the efficacy of R-maintenance in MRD-negative patients appeared less prominent than after R-CHOP in pooled PB/BM (HR, 0.57 [95% CI, 0.28 to 1.16]; n = 44; Fig 3E), PB (HR, 0.51 [95% CI, 0.25 to 1.05]; n = 43; Data Supplement, Fig S2E), and BM (HR, 0.34 [95% CI, 0.13 to 0.89]; n = 27; Data Supplement, Fig S3E). Since very few evaluable patients after R-FC were MRD-positive, the efficacy of R-maintenance was not interpretable in this patient group (Fig 3F), and the overall results were mainly driven by MRD-negative patients.

MRD Conversion During Maintenance

To investigate MRD patterns in PB during the first 2 years of maintenance, we analyzed 88 patients randomly assigned to and treated with maintenance who had at least three available MRD samples (Data Supplement, Table S3). Among 55 patients treated with R-maintenance (38 MRD-negative at EOI), 53% remained constantly MRD-negative, 15% converted to MRD negativity (during the first year), and 4% converted to MRD positivity (during the second year). In addition, 7% remained MRD-positive and 22% of patients had an alternating MRD pattern. In comparison, among 33 patients treated with IFN maintenance (27 MRD-negative at EOI), 42% remained MRD-negative, 3% converted to MRD negativity and conversions to MRD positivity were seen in 24% (5/8 during the first year). In addition, 6% remained MRD-positive and 24% had an alternating MRD pattern (P = .028). These results suggest that R-maintenance is associated with sustained MRD negativity and has the potential to induce MRD conversions from positive to negative.

Prognostic Value of MRD Status

MRD status at MI was prognostic for achieving CR at EOI (Data Supplement, Results and Table S4). At MI and EOI, MRD positivity after R-CHOP in pooled PB/BM was not clearly associated with inferior TTP (Figs 4A and 4B; Data Supplement, Fig S5), in contrast to R-FC (Figs 5A and 5B). Of note, TTP after MRD negativity and after MRD positivity differed remarkably depending on the type of induction treatment (Data Supplement, Figs S6A and S6C), also in patients without subsequent R-maintenance (Data Supplement, Figs S6B and S6D).

After R-CHOP, MRD positivity in PB during the 6-month period before the landmarks 6/12/18/24 months after EOI was associated with shorter TTP, also when adjusted for MIPI score, clinical response, and maintenance (Figs 4C-4F). Remarkably, median times from MRD positivity to clinical progression decreased with increasing time since EOI (landmarks 6/12/18/24 months: 2.3/1.7/1.7/1.4 years). After R-FC, MRD status was consistently prognostic for subsequent TTP (Figs 5C-5F) and median times from MRD positivity to progression were short (landmarks 6/12/18/24 months: 1.1/1.0/0.7/0.7 years).

DISCUSSION

We performed a comprehensive analysis of MRD data from the MCL Elderly trial of the European MCL network. In addition to the known prognostic role of MRD in MCL, our results show how MRD information can affect treatment decisions and future research. Most current approaches to integrate MRD into novel treatment strategies focus on reducing treatment in MRD-negative patients (eg, ClinicalTrials.gov identifiers: NCT03267433, NCT05214183, and NCT04624958), following the assumption that the risk of progression in good responders could not be modified by further postinduction treatment. We found that the efficacy of R-maintenance was clearly confirmed in MRD-negative patients after R-CHOP induction by substantially prolonged PFS and OS. Our results are in line with observations from the LYSA-LYMA trial in younger patients with MCL, where almost all patients were MRD-negative after high-dose cytarabine-containing induction and ASCT so that one can conclude that the improvement of PFS and OS by

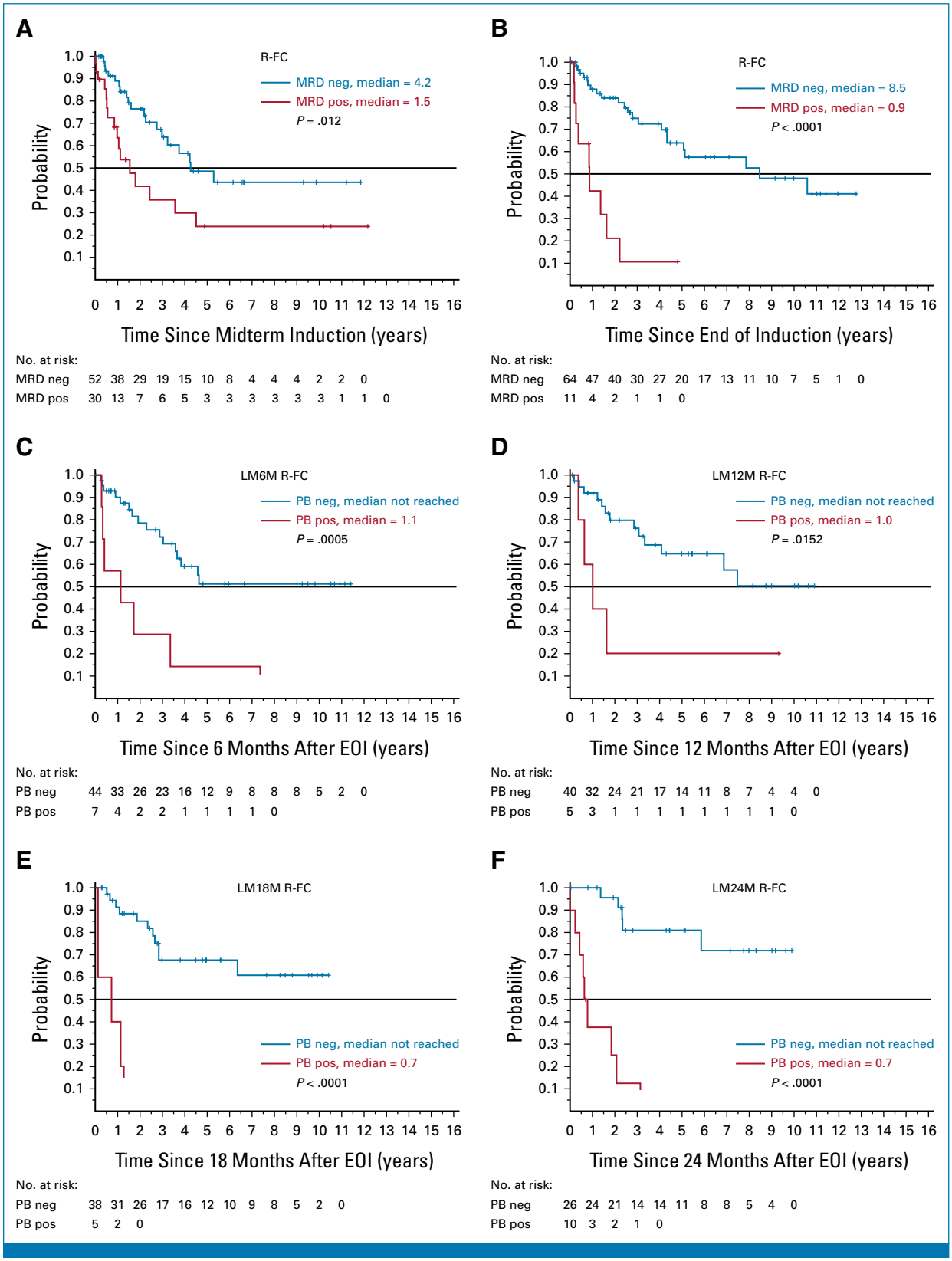

FIG 5. Prognostic value of MRD status for time to progression from (A) MI, (B) EOI, and (C-F) from landmark time points 6/12/18/24 months after EOI in R-FC group among patients progression-free up to the landmark. (A) Time to progression according to MRD status at MI pooled from PB and BM, HR (95% CI) adjusted for MIPI score: 2.53 (1.29 to 4.98); (B) time to progression according to MRD status at EOI pooled from PB and BM, HR (95% CI) adjusted for MIPI score, clinical remission, and maintenance 4.84 (1.83 to 12.78); (C-F) time to progression according to MRD status in PB before the LM time point (continued on following page)

FIG 5. (Continued). (C) 6/(D) 12/(E) 18/(F) 24 months from EOI, HRs (95% CI) adjusted for MIPI score, clinical remission, and maintenance (C) 5.13 (1.40 to 18.83), (D) 3.14 (0.94 to 10.48), (E) 12.64 (3.08 to 52), and (F) 35.6 (4.95 to 257). To assess the prognostic effects of MRD status on time to clinical progression, death in clinical remission was censored. BM, bone marrow; EOI, end of induction; HR, hazard ratio; LM, landmark; M, month from EOI; MI, midterm induction; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, minimal residual disease; neg, negative; PB, peripheral blood; pos, positive (including both, MRD-positive below quantifiable range and positive quantifiable); R-FC, rituximab, fludarabine, cyclophosphamide.

R-maintenance was mainly based on MRD-negative patients.[22] As a consequence, treatment de-escalation by omitting R-maintenance in MRD-negative patients is strongly discouraged. This is consistent with results in FL from the randomized FIL-FOLL12 trial, showing that omitting R-maintenance in patients with MRD negativity and complete metabolic response resulted in inferior PFS.[23]

In patients who are MRD-positive at EOI, the efficacy of R-maintenance appeared reduced. Thus, a low-level residual tumor load seems to be a prerequisite for effective disease control by R-maintenance. Our findings decipher the role of MRD response as a surrogate for maintenance treatment efficacy, implying that postinduction treatment with an effective drug should be part of the treatment concept in patients with MCL.

Induction with 6× R-FC achieved more frequent and earlier MRD clearance than 8× R-CHOP, with less frequently quantifiable MRD positivity. Competing risk analyses had shown that R-FC achieved long-term lymphoma control but was associated with a high risk of nonlymphoma-related deaths, especially in patients receiving R-maintenance.[7] The MRD results may thus appear contradictory to the clinical results, but they mainly show that MRD cannot capture potential toxic effects of a given treatment.

In landmark analyses up to 24 months from EOI, the prognostic value of MRD status in PB for subsequent clinical progression was clearly demonstrated in both induction arms. Of note, times from MRD positivity to clinical progression were rather short with time intervals of 1-1.7 years after R-CHOP and even shorter after R-FC. Thus, MRD positivity in clinical remission after cytoreductive treatment emerges as an important trigger for treatment intensification. Recently, Ferrero et al[24] performed a comprehensive MRD analysis in patients with MCL enrolled in a trial assessing lenalidomide maintenance versus observation after ASCT. In line with our results, the risk of relapse gradually increased over time, along with the persistence of MRD positivity in BM.[24]

After intensive treatments such as R-DHAP followed by ASCT in younger patients[5,22] and in the analysis by Ferrero et al,[24] MRD status at early time points was shown to be prognostic for early progression and long-term outcome. In contrast, in our cohort, MRD status at the end of R-CHOP induction lacked a clear prognostic value but was strongly prognostic during and at the end of R-FC and at landmark analyses after start of maintenance. The prognosis for both MRD-positive and MRD-negative patients clearly depended on the type of induction chemotherapy, suggesting a differential impact of chemotherapy on the depth of response, thereby modifying the prognostic effect of MRD status.

One further reason why MRD status after R-CHOP was not prognostic at EOI might be the rather small number of BM samples analyzed, known as the more sensitive compartment for MRD detection. Although BM samples were requested regularly per protocol during follow-up, these samples were not frequently collected. This is particularly important as the comparative analysis of Ferrero et al[24] has shown that in single time point analysis, BM outperformed PB samples with respect to prognostication. In our cohort, the direct comparison of MRD-clearance in PB and BM by induction showed that only up to 15% of MRD-positive patients are missed when only PB is analyzed. During follow-up, we restricted all results to PB samples most closely reflecting future clinical practice because regular BM samples might be not widely accepted.

In this trial, MRD was assessed by qPCR, a method that used to be the gold standard when the study was planned.[25] The fact that only 80% of patients with diagnostic samples scheduled for MRD assessment were finally evaluable was mainly due to low-infiltrated diagnostic samples (PB and/or BM) that resulted in either failure to detect a clonal marker (15%) or missing the EuroMRD criteria of technical requirements for limits of sensitivity and quantification (5%). This observation was also made by Ferrero et al.[24] Therefore, for prospective design of MRD-guided trials, one would include FFPE-tissue to increase the number of evaluable patients to >90%. Besides a dropout rate of approximately 20%, qPCR has the drawback that a considerable amount of MRD-positive samples do not give quantifiable MRD levels. Other methods such as ddPCR[21] and particularly next-generation sequencing[26] will overcome limitations of qPCR[25] and will improve feasibility of MRD assessment for clinical decision making. In the meantime, qPCR results as those established here should serve as a strong reference.

In conclusion, MRD status by qPCR was confirmed as a strong predictor of treatment efficacy and subsequent clinical progression. Our results confirm the importance of R-maintenance in patients with MCL and conclusively show that treatment de-escalation by omitting R-maintenance in MRD-negative patients cannot be recommended. In contrast, intensified maintenance for MRD-positive patients after induction, including additive treatments as soon as

MRD persistence or reappearance is observed, should be investigated in the context of clinical trials. Furthermore, beyond the application for pure prognostic purposes, our results show the utility of and advocate for the assessment of MRD for treatment efficacy monitoring and establishing novel risk-adapted treatment strategies.

AFFILIATIONS

[1]Institute for Medical Informatics, Biometry, and Epidemiology (IBE), LMU Munich, Munich, Germany
[2]Department of Internal Medicine III, University Hospital LMU Munich, Munich, Germany
[3]Department of Immunobiology and Inserm U955, Université Hôpital Henri Mondor, Créteil, France
[4]Laboratory of Onco-Hematology, Université Paris Cité, Institut Necker-Enfants Malades and Assistance Publique-Hôpitaux de Paris, Paris, France
[5]Department of Internal Medicine III, University of Ulm, Ulm, Germany
[6]VK&K Studien GbR, Landshut, Germany
[7]Hospices Civils de Lyon, Université Claude Bernard, Centre Hospitalier Lyon-Sud, Pierre Bénite, France
[8]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[9]Department of Hematology, Hôpital Saint Louis, Paris, France
[10]Department of Hematology and U1245, Centre Henri Becquerel, Rouen, France
[11]Department of Medicine II, University of Tübingen, Tübingen, Germany
[12]Department of Hematology and INSERM 1256, University of Lorraine, Vandoeuvre les Nancy, France
[13]Klinik I für Innere Medizin, Universität zu Köln, Köln, Germany
[14]Institut Gustave Roussy, Villejuif, France
[15]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[16]Department of Medicine, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany

CORRESPONDING AUTHOR

Christiane Pott, MD, PhD, Medizinische Klinik II, Hämatologie und Internistische Onkologie Universitätsklinikum Schleswig-Holstein, Campus Kiel, Arnold-Heller Strasse 3, 24105 Kiel, Germany; e-mail: c.pott@med2.uni-kiel.de.

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CLINICAL TRIAL INFORMATION

NCT00209209 (MCL Elderly)

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DATA SHARING STATEMENT

Data on minimal residual disease and clinical data underlying this manuscript will be shared on request to the corresponding author on the basis of a scientific collaboration.

AUTHOR CONTRIBUTIONS

Conception and design: Eva Hoster, Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Martin Dreyling, Christiane Pott
Financial support: Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Martin Dreyling, Christiane Pott
Administrative support: Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Martin Dreyling, Christiane Pott
Provision of study materials or patients: Stephan Stilgenbauer, Ursula Vehling-Kaiser, Gilles Salles, Catherine Thieblemont, Hervé Tilly, Stefan Wirths, Pierre Feugier, Kai Hübel, Christian Schmidt, Vincent Ribrag, Johanna C. Kluin-Nelemans, Martin Dreyling, Christiane Pott
Collection and assembly of data: Eva Hoster, Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Stephan Stilgenbauer, Ursula Vehling-Kaiser, Gilles Salles, Catherine Thieblemont, Hervé Tilly, Stefan Wirths, Pierre Feugier, Kai Hübel, Christian Schmidt, Vincent Ribrag, Johanna C. Kluin-Nelemans, Martin Dreyling, Christiane Pott
Data analysis and interpretation: Eva Hoster, Marie-Hélène Delfau-Larue, Elizabeth Macintyre, Linmiao Jiang, Stephan Stilgenbauer, Gilles Salles, Catherine Thieblemont, Vincent Ribrag, Johanna C. Kluin-Nelemans, Martin Dreyling, Christiane Pott
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Predictive Value of Minimal Residual Disease for Efficacy of Rituximab Maintenance in Mantle Cell Lymphoma: Results From the European Mantle Cell Lymphoma Elderly Trial

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Marie-Hélène Delfau-Larue
Honoraria: Gilead Sciences, Amgen, Takeda
Consulting or Advisory Role: Caribou Biosciences, Inc
Research Funding: Roche (Inst), Celgene (Inst)
Travel, Accommodations, Expenses: Anssen-Cilag

Elizabeth Macintyre
Employment: Owkin
Honoraria: Astra Zeneca and Janssen
Research Funding: Celgene/Bristol Myers Squibb
Patents, Royalties, Other Intellectual Property: Collective patent on lymphoid clonality diagnostics with the Euro-Clonality group
Other Relationship: President of the European Hematology Association

Stephan Stilgenbauer
Honoraria: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen, BeiGene, Novartis, Bristol Myers Squibb/Pfizer
Consulting or Advisory Role: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen, Novartis, BeiGene, Bristol Myers Squibb/Pfizer
Speakers' Bureau: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen, Bristol Myers Squibb/Pfizer, Novartis, BeiGene
Research Funding: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen, BeiGene, Bristol Myers Squibb/Pfizer, Novartis
Travel, Accommodations, Expenses: AbbVie, AstraZeneca, Celgene, Gilead Sciences, GlaxoSmithKline, Roche, Janssen, Novartis, BeiGene, Bristol Myers Squibb/Pfizer

Ursula Vehling-Kaiser
Consulting or Advisory Role: Hexal, Roche, Gilead Sciences, Lilly, AbbVie, Amgen
Speakers' Bureau: Hexal, Merck Sharp & Dohme, Sirtex Medical, MorphoSys, Forum for Medical Futher Education, Jürgen Schaaf Verlags, Gilead Sciences, CSL Behring, Boehringer Ingelheim, Roche, OnkoInform, Lilly, Merck Serono, AbbVie, Octapharm, Amgen

Gilles Salles
Stock and Other Ownership Interests: Owkin
Honoraria: AbbVie, Incyte
Consulting or Advisory Role: Roche/Genentech, Janssen, Novartis, Morphosys, Epizyme, Genmab, Debiopharm Group, BMS, BeiGene, Incyte, Ipsen, AbbVie, Kite/Gilead, Loxo/Lilly, Molecular Partners, Nordic Nanovector, ATB Therapeutics, Merck, Orna Therapeutics, Nurix
Research Funding: 0920 (Inst), Janssen (Inst), Ipsen (Inst)

Catherine Thieblemont
Honoraria: Celgene, AbbVie, Bayer, Janssen, Roche, Incyte, Novartis, Gilead Sciences
Research Funding: Roche
Travel, Accommodations, Expenses: Roche, Janssen-Cilag, Kite/Gilead, Novartis, AbbVie

Hervé Tilly
Honoraria: Bristol Myers Squibb, Roche
Consulting or Advisory Role: Roche, Incyte, Celgene/Bristol Myers Squibb, ADC Therapeutics
Research Funding: Roche/Genentech (Inst)
Travel, Accommodations, Expenses: Janssen, Gilead Sciences

Stefan Wirths
Honoraria: AbbVie, Roche Pharma AG, AstraZeneca
Speakers' Bureau: Stemline Therapeutics (Inst)
Expert Testimony: Stemline Therapeutics
Travel, Accommodations, Expenses: BeiGene, AbbVie

Pierre Feugier
Honoraria: Roche/Genentech, Janssen, Gilead Sciences, Amgen, AbbVie, AstraZeneca, BeiGene
Consulting or Advisory Role: Roche/Genentech, Janssen, AbbVie, Gilead Sciences, Amgen, AstraZeneca
Speakers' Bureau: Roche/Genentech, AbbVie, Amgen, Janssen, Gilead Sciences
Research Funding: Roche/Genentech, Gilead Sciences, Janssen, AbbVie, Amgen
Travel, Accommodations, Expenses: Amgen, Gilead Sciences, Janssen, Roche/Genentech, AbbVie

Kai Hübel
Consulting or Advisory Role: Roche, Incyte, EUSA Pharma, AbbVie, Novartis, Sandoz/Hexal, Gilead Sciences, BMS, BeiGene
Speakers' Bureau: Roche, Incyte, EUSA Pharma, Novartis, AbbVie, BeiGene
Research Funding: Incyte (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Roche

Christian Schmidt
Honoraria: AstraZeneca, Roche/Genentech
Consulting or Advisory Role: Kite/Gilead, Novartis, Bristol Myers Squibb, Janssen
Travel, Accommodations, Expenses: Kite/Gilead, BeiGene, Janssen

Vincent Ribrag
Honoraria: AZD, Infinity Pharmaceuticals, Gilead Sciences, NanoString Technologies, Roche, Novartis, AbbVie
Consulting or Advisory Role: Infinity Pharmaceuticals, PharmaMar, Gilead Sciences, NanoString Technologies, Bristol Myers Squibb, MSD, Roche/Genentech, Immune Design, Roche, Incyte
Research Funding: arGEN-X BVBA, Epizyme (Inst), Argenx (Inst), Astex Pharmaceuticals (Inst), GlaxoSmithKline/Adaptimmune (Inst)
Expert Testimony: Servier
Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb, AZD

Martin Dreyling
Consulting or Advisory Role: Acerta Pharma/AstraZeneca, Celgene/Jazz, Gilead Sciences, Janssen-Cilag, Novartis, Roche, Beigene, AbbVie/Genentech (Inst), Lilly Medical
Speakers' Bureau: Gilead Sciences, Janssen-Cilag, Roche Pharma AG, Beigene, Lilly, Novartis, AstraZeneca
Research Funding: Celgene (Inst), Janssen-Cilag (Inst), Roche Pharma AG (Inst), AbbVie (Inst), Bayer (Inst), Kite/Gilead (Inst)
Travel, Accommodations, Expenses: Celgene, Janssen-Cilag, Roche Pharma AG

Christiane Pott
Honoraria: Roche Pharma AG
Speakers' Bureau: Roche Pharma AG
Research Funding: Roche/Genentech

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