JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Confirmation of the Mantle-Cell Lymphoma International Prognostic Index in Randomized Trials of the European Mantle-Cell Lymphoma Network

*Eva Hoster, Wolfram Klapper, Olivier Hermine, Hanneke C. Kluin-Nelemans, Jan Walewski, Achiel van Hoof, Marek Trneny, Christian H. Geisler, Francesco Di Raimondo, Michal Szymczyk, Stephan Stilgenbauer, Catherine Thieblemont, Michael Hallek, Roswitha Forstpointner, Christiane Pott, Vincent Ribrag, Jeanette Doorduijn, Wolfgang Hiddemann, Martin H. Dreyling, and Michael Unterhalt*

Eva Hoster, Roswitha Forstpointner, Wolfgang Hiddemann, Martin H. Dreyling, and Michael Unterhalt, University Hospital Munich; Eva Hoster, University of Munich, Munich; Wolfram Klapper, University of Kiel; Christiane Pott, University Hospital Schleswig-Holstein, Kiel; Michael Hallek, Universität Köln, Köln; Stephan Stilgenbauer, University of Ulm, Ulm, Germany; Olivier Hermine, University Paris Descartes and Université Sorbonne Paris Cité; Catherine Thieblemont, Hôpital Saint Louis, Paris; Vincent Ribrag, Institut Gustave Roussy, Villejuif, France; Hanneke C. Kluin-Nelemans, University of Groningen, Groningen; Jeanette Doorduijn, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; Jan Walewski and Michal Szymczyk, Maria Sklodowska-Curie Memorial Institute, Warsaw, Poland; Achiel van Hoof, A. Z. Sint Jan AV, Brugge, Belgium; Marek Trneny, Charles University General Hospital, Prague, Czech Republic; Christian H. Geisler, Rigshospitalet, Copenhagen, Denmark; and Francesco Di Raimondo, University of Catania, Italy.

Published online ahead of print at www.jco.org on March 31, 2014.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Eva Hoster, PhD, Department of Internal Medicine III, University Hospital Munich, Marchioninistr. 15, 81377 Munich, Germany; e-mail: Eva.Hoster@med.uni-muenchen.de.



0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2013.52.2466

## ABSTRACT

### Purpose
Mantle-cell lymphoma (MCL) is a distinct B-cell lymphoma associated with poor outcome. In 2008, the MCL International Prognostic Index (MIPI) was developed as the first prognostic stratification tool specifically directed to patients with MCL. External validation was planned to be performed on the cohort of the two recently completed randomized trials of the European MCL Network.

### Patients and Methods
Data of 958 patients with MCL (median age, 65 years; range, 32 to 87 years) treated upfront in the trials MCL Younger or MCL Elderly were pooled to assess the prognostic value of MIPI with respect to overall survival (OS) and time to treatment failure (TTF).

### Results
Five-year OS rates in MIPI low, intermediate, and high-risk groups were 83%, 63%, and 34%, respectively. The hazard ratios for OS of intermediate versus low and high versus intermediate risk patients were 2.1 (95% CI, 1.5 to 2.9) and 2.6 (2.0 to 3.3), respectively. MIPI was similarly prognostic for TTF. All four clinical baseline characteristics constituting the MIPI, age, performance status, lactate dehydrogenase level, and WBC count, were confirmed as independent prognostic factors for OS and TTF. The validity of MIPI was independent of trial cohort and treatment strategy.

### Conclusion
MIPI was prospectively validated in a large MCL patient cohort homogenously treated according to recognized standards. As reflected in current guidelines, MIPI represents a generally applicable prognostic tool to be used in research as well as in clinical routine, and it can help to develop risk-adapted treatment strategies to further improve clinical outcome in MCL.

*J Clin Oncol 32. © 2014 by American Society of Clinical Oncology*

## INTRODUCTION

Since 1994, mantle-cell lymphoma (MCL) has been recognized worldwide as a distinct subtype of malignant B-cell lymphoma in the Revised European-American Lymphoma classification,[1] now incorporated in the current WHO classification.[2] The introduction of cyclin D1 in immunohistochemistry has facilitated accurate histological diagnosis. With an age-adjusted incidence of approximately 0.6 per 100,000 person-years and accounting for approximately 3% of non-Hodgkin lymphomas in the United States,[3] MCL is relatively rare. Although the prognosis has improved during the last decades,[4] MCL remains incurable, with a relatively short survival compared with follicular lymphoma.

In 2008, the MCL International Prognostic Index (MIPI)[5] was developed to identify clinical prognostic factors and patient risk groups with different courses of disease. As the first prognostic index specific for MCL, it was derived from data of more than 400 patients with MCL, treated in randomized trials of the German Low-Grade Lymphoma Study Group and the European MCL Network. Along with model development, internal bootstrap validation had been performed, and external validation was planned to be done by using pooled data of the recently completed trials of the European MCL Network, MCL Younger[6,7] (NCT00209222) and MCL Elderly[8] (NCT00209209). After randomization was stopped in these trials, we investigated the prognostic value of MIPI in this large independent prospective patient cohort.

## PATIENTS AND METHODS

### Patients

Previously untreated adult patients qualified for the trials if they had histologically confirmed MCL of Ann Arbor stages II to IV and an Eastern Cooperative Oncology Group performance status (ECOG PS)[9] up to 2. Histological diagnosis was centrally reviewed by the European MCL Pathology Panel. In MCL Younger, patients up to 65 years suitable for high-dose treatment received six cycles induction therapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or alternating R-CHOP and rituximab plus dexamethasone, cytarabine, and cisplatin (R-DHAP), followed by high-dose radiochemotherapy and peripheral-blood stem-cell transplantation in remission.[6] In MCL Elderly, treatment for patients older than 60 years not suitable for high-dose therapy consisted of eight cycles of R-CHOP or six cycles of rituximab plus fludarabine and cyclophosphamide, followed by maintenance with rituximab or interferon-alfa in remission.[8] Both trials were performed in accordance with the declaration of Helsinki, and all patients had given written informed consent.

### MIPI and Outcome Parameters

MIPI score was calculated as the weighted sum of the baseline values for the MIPI factors, age, ECOG PS, lactate dehydrogenase (LDH) activity as quotient to the upper limit of normal, and WBC count per $10^{-6}$L, according to the following formula:

$$\text{MIPI score} = 0.03535 \times \text{age (years)} + 0.6978 \text{ (if ECOG PS} > 1\text{, otherwise 0)} + 1.367 \times \log_{10}(\text{LDH/upper limit of normal}) + 0.9393 \times \log_{10}(\text{WBC count per } 10^{-6}\text{L}).[5]$$

Patients with MIPI score $< 5.70$ were classified as low risk (LR), patients with MIPI score $\geq 5.70$ but $< 6.20$ as intermediate risk (IR), and patients with MIPI score $\geq 6.20$ as high risk (HR).[5]

In addition, we calculated the simplified MIPI (s-MIPI; Data Supplement),[5] which had been developed as a surrogate for MIPI to allow a bedside application when a calculator is not available, and the biologic MIPI (MIPI-b),[5] which combines the MIPI score with the rate of proliferating tumor cells (protein encoded by the *MKI76* gene [Ki-67] index). The Ki-67 index had been assessed on diagnostic tumor biopsies by the European MCL Pathology Panel according to its published guideline.[10]

For the present evaluation, the primary outcome parameter was overall survival (OS) from trial registration to death from any cause, censored at the latest follow-up if patients were alive. Secondary outcome parameters were complete remission (CR) and overall response rates (ORRs)[11] after induction, and time to treatment failure (TTF) from treatment start to nonresponse, progression, or death from any cause, censored at the latest tumor assessment if progression was excluded. The date of nonresponse was the last day of induction.

### Statistical Methods

A minimum number of 40 events was necessary[12] to detect survival differences with hazard ratios of 1.90 for IR versus LR and 2.44 for HR versus IR, as observed in the original data set,[5] with 95% probability by a three-group comparison with the log-rank test at a significance level of 5%. To detect smaller hazard ratios (1.5 and 2.0, respectively), 76 events were needed. OS and TTF, stratified according to MIPI, s-MIPI, or MIPI-b, were described with Kaplan-Meier estimates and compared by log-rank tests. Cox regression was used to assess hazard ratios between risk groups with 95% CIs and the prognostic impact of MIPI score, MIPI factors, and Ki-67 index. Cumulative incidence rates (CIRs) of nonresponse or progression, treating death without progression as competing event, were calculated and compared by Gray's test.[13] We used the c-index[14] to compare the prognostic discrimination of MIPI, s-MIPI, and MIPI-b. We additionally performed analyses stratified according to trials, treatment, or age groups. Reported *P* values are two-sided. For external validation, we selected patients with MCL of advanced stages III or IV as in the original data set.[5] By including patients of all stages, we explored the additional prognostic value of advanced stage. The concordance of MIPI and s-MIPI was assessed by weighted kappa.[15]

## RESULTS

### Patient Cohort

Of 1,057 patients randomly assigned in MCL Younger and MCL Elderly from January 2004 to October 2010, 41 (4%) did not have MCL after pathology review, and 7 (1%) had no follow-up. Four patients had stage I and 47 patients had stage II disease, resulting in 958 patients included in the validation cohort (Data Supplement).

Median age was 65 years (range, 32 to 87 years), 74% were male, 87% had Ann Arbor stage IV, 39% B-symptoms, 7% ECOG PS 2, 42% elevated LDH, and median WBC count was 7.7 per $10^{-9}$L (Table 1). After a median observation time of 4 years, 316 patients had died, reflected in a 5-year OS of 61%; 474 patients had experienced a treatment failure resulting in a 5-year TTF of 40%.

### MIPI and OS

According to MIPI, 33% of patients were classified as LR, 32% as IR, and 35% as HR. In the LR, IR, and HR groups, 5-year OS rates were 83%, 63%, and 34%, respectively ($P < .001$; Fig 1A). The hazard ratios of IR versus LR and HR versus IR patients were 2.1 (95% CI, 1.5 to 2.9; $P < .001$) and 2.6 (2.0 to 3.3; $P < .001$). All MIPI factors revealed independent prognostic impact with hazard ratios 1.6 for a 10-year increase of age, 1.9 for ECOG PS 2, 2.0 for twofold LDH, and 1.9 for 10-fold WBC count (Table 2).

### MIPI and TTF

Five-year TTF rates in LR, IR, and HR groups were 59%, 37%, and 22%, respectively ($P < .001$; Fig 1B). We estimated hazard ratios of 1.6 (1.3 to 2.1; $P < .001$) for IR versus LR, and 2.1 (1.7 to 2.5; $P < .001$) for HR versus IR groups. All MIPI factors revealed independent prognostic impact on TTF with hazard ratios 1.5 for a 10-year increase of age, 2.1 for ECOG PS 2, 1.7 for twofold LDH, and 1.4 for 10-fold WBC count (Table 2). The 5-year CIR of nonresponse or progression was 35%, 56%, and 62% for MIPI LR, IR, and HR patients, respectively ($P < .001$; Data Supplement). In MIPI LR, IR, and HR groups, ORRs were 94%, 89%, and 75%, respectively ($P < .001$; Table 3). CR rates were comparable in MIPI LR and IR groups (50% and 51%), but lower in the HR group (40%; $P = .014$).

### MIPI and Trial Cohort

Patients of MCL Younger were younger, had better performance status, and lower LDH, but similar WBC count compared with MCL Elderly patients (Table 1). Consequently, MCL Younger patients had a more favorable MIPI risk profile (61% LR, 24% IR, and 14% HR) compared with MCL Elderly patients (8% LR, 39% IR, and 53% HR).

Among MCL Younger patients, 5-year OS rates according to MIPI were 84%, 58%, and 40% ($P < .001$; Fig 1C), respectively, and hazard ratios for IR versus LR and HR versus IR were 2.7 (1.8 to 4.2) and 1.7 (1.1 to 2.7), respectively. Five-year TTF rates according to MIPI were 60%, 34%, and 34%, respectively, with a median TTF of 6.3, 3.7, and 2.1 years, respectively ($P < .001$; Fig 1D). All MIPI factors but performance status had independent effects on OS and TTF among MCL Younger patients (Table 2). In MIPI LR, IR, and HR

**Table 1.** Patient Demographics and Clinical Characteristics

| Characteristic | Pooled Trials (n = 958) No. | % | MCL Younger (n = 454; 47%) No. | % | MCL Elderly (n = 504; 53%) No. | % | P* |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | < .001 |
| Median | 65 | | 55 | | 70 | | |
| Range | 32-87 | | 32-66 | | 60-87 | | |
| Male | 710 | 74 | 358 | 79 | 352 | 70 | .001 |
| Stage IV | 837 | 87 | 392 | 86 | 445 | 88 | .38 |
| B-symptoms | 371 | 39 | 174 | 38 | 197 | 39 | .84 |
| ECOG PS 2 | 63 | 7 | 20 | 4 | 43 | 9 | .013 |
| Elevated LDH | 399 | 42 | 170 | 37 | 229 | 45 | .013 |
| LDH/ULN | | | | | | | .010 |
| Median | 0.94 | | 0.92 | | 0.97 | | |
| Range | 0.29-12.2 | | 0.29-12.2 | | 0.29-11.3 | | |
| WBC count ($10^9$/L) | | | | | | | .20 |
| Median | 7.7 | | 7.6 | | 7.9 | | |
| Range | 1.1-396 | | 1.1-388 | | 1.1-396 | | |
| MIPI | | | | | | | |
| LR | 318 | 33 | 279 | 61 | 39 | 8 | < .001 |
| IR | 307 | 32 | 110 | 24 | 197 | 39 | |
| HR | 333 | 35 | 65 | 14 | 268 | 53 | |
| MIPI score | | | | | | | < .001 |
| Median | 5.97 | | 5.59 | | 6.23 | | |
| Range | 4.07-8.68 | | 4.07-8.68 | | 4.97-8.52 | | |
| s-MIPI | | | | | | | |
| LR | 308 | 32 | 243 | 54 | 65 | 13 | < .001 |
| IR | 345 | 36 | 134 | 30 | 211 | 42 | |
| HR | 305 | 32 | 77 | 17 | 228 | 45 | |
| Ki-67 index (%)† | | | | | | | .38 |
| Median | 20 | | 20 | | 20 | | |
| Range | 2-97 | | 2-97 | | 2-91 | | |
| MIPI-b | | | | | | | |
| LR | 76 | 16 | 76 | 31 | 0 | 0 | < .001 |
| IR | 214 | 46 | 116 | 47 | 98 | 44 | |
| HR | 180 | 38 | 57 | 23 | 123 | 56 | |
| MIPI-b score | | | | | | | < .001 |
| Median | 6.30 | | 5.94 | | 6.56 | | |
| Range | 4.94-10.53 | | 4.94-10.53 | | 5.75-9.54 | | |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status[9]; HR, high risk; IR, intermediate risk; Ki-67, protein encoded by the *MKI76* gene; LDH, lactate dehydrogenase; LR, low risk; MCL, mantle-cell lymphoma; MIPI, MCL International Prognostic Index; MIPI-b, biologic MIPI; s-MIPI, simplified MIPI; ULN, upper limit of normal.
*P value for the comparison of MCL Younger and MCL Elderly.
†Ki-67 index evaluated on 470 samples: MCL Younger, 249; MCL Elderly, 221.

groups, ORRs were 94%, 90%, and 83%, respectively, ($P = .014$), and CR rates were 48%, 45%, and 38%, respectively ($P = .38$; Table 3).

In MCL Elderly, 5-year OS rates according to MIPI were 76%, 66%, and 32%, respectively, ($P < .001$; Fig 1E), and hazard ratios for IR versus LR and HR versus IR were 1.1 (0.5 to 2.3) and 3.1 (2.2 to 4.3), respectively. Five-year TTF rates according to MIPI were 49%, 40%, and 19%, respectively ($P < .001$; Fig 1F); ORRs were 95%, 89%, and 73%, respectively ($P < .001$); and CR rates were 62%, 54%, and 41%, respectively ($P = .003$; Table 3). MIPI score and all four MIPI factors were highly prognostic for OS and TTF also among MCL Elderly patients (Table 2). Similarly, we confirmed the prognostic value of MIPI in age groups younger than or older than 60 years (Data Supplement).

### MIPI and Treatment

The results of MCL Elderly[8] have led to the conclusion that R-CHOP followed by rituximab maintenance should be the new standard for patients with MCL not eligible for high-dose treatment, whereas in MCL Younger, the introduction of high-dose cytarabine into induction and high-dose treatment has shown a prolongation of TTF,[6] and, potentially, OS.[7] Therefore, we investigated the prognostic value of MIPI in two subcohorts pooled from both trials representing the pretrials standards (R-CHOP followed by autologous stem-cell transplantation [ASCT] or interferon-alfa maintenance), and the superior treatment arms (R-CHOP/R-DHAP alternating followed by ASCT or R-CHOP followed by rituximab maintenance), respectively.

In patients treated according to the pretrials standards, MIPI groups revealed different OS (Fig 2A) and TTF (Fig 2B). Among patients pooled from the trials' superior treatment arms, MIPI again separated LR, IR, and HR groups with regards to OS (Fig 2C) and TTF (Fig 2D).

### MIPI-b

The median Ki-67 index, counted on diagnostic biopsies of 470 patients with MCL, was 20% (2% to 97%). The Ki-67 index was prognostic for OS in univariable analysis and adjusted for

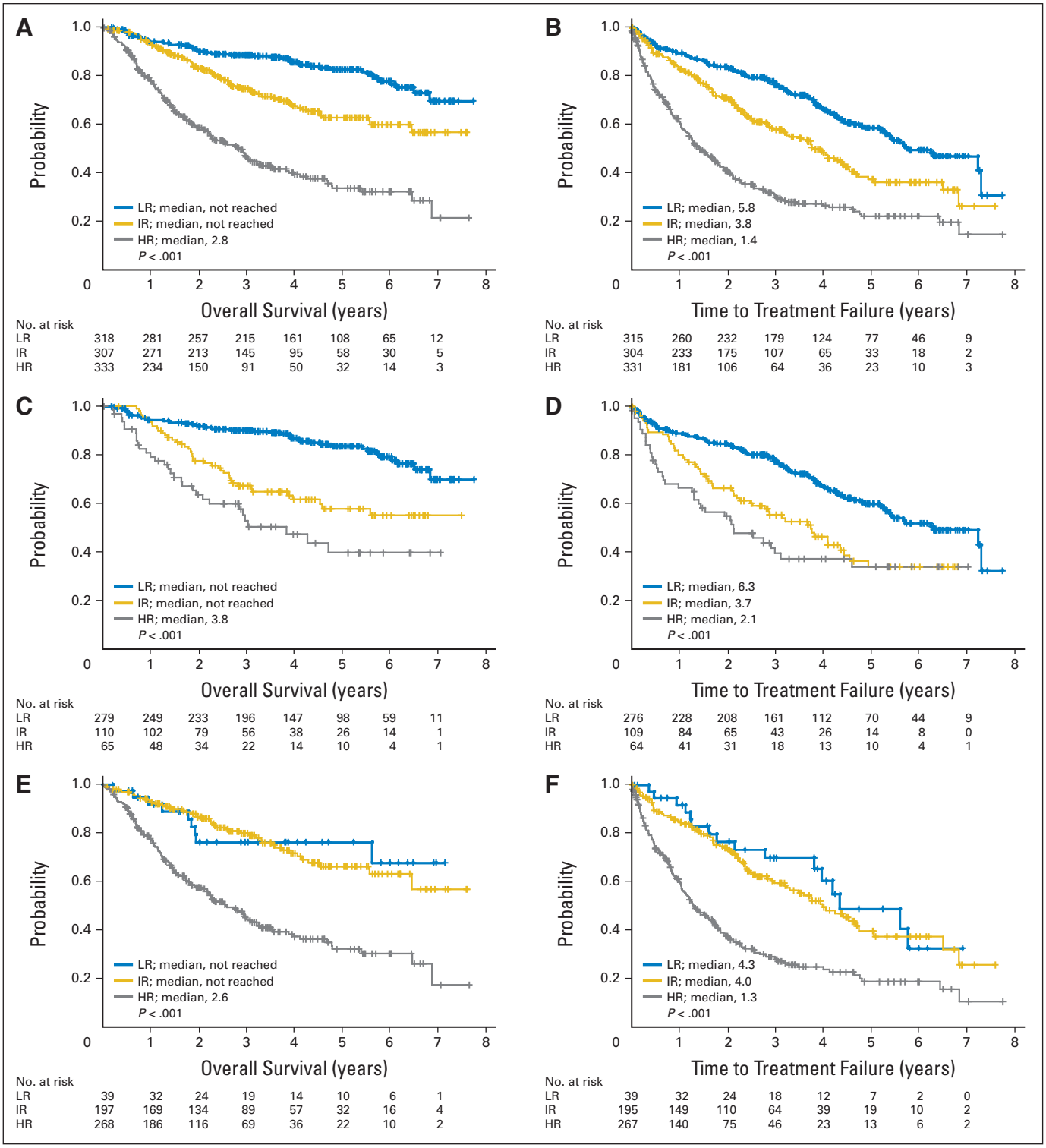


**Fig 1.** Overall survival (OS) and time to treatment failure (TTF) according to the Mantle-Cell Lymphoma (MCL) International Prognostic Index (MIPI) in pooled trials and stratified by trial cohort. (A) OS in pooled trials (54, 88, and 174 events in low risk [LR], intermediate risk [IR], and high risk [HR] groups, respectively). (B) TTF in pooled trials (115, 140, and 219 events, respectively). (C) OS in MCL Younger (45, 41, and 31 events, respectively), (D) TTF in MCL Younger (99, 57, and 38 events, respectively), (E) OS in MCL Elderly (9, 47, and 143 events, respectively), and (F) TTF in MCL Elderly (16, 83, and 181 events, respectively). The interaction *P* values of MIPI risk groups and trial cohort were .041 for OS and .051 for TTF.

MIPI score (adjusted hazard ratio, 1.15; 95% CI, 1.08 to 1.24; $P < .001$; Data Supplement).

According to MIPI-b, 16% of 470 patients were classified as LR, 46% as IR, and 38% as HR (Table 1). OS was comparable in patients with LR or IR according to MIPI-b (5-year OS 81% and 83%, respectively), but markedly different to HR patients (5-year OS, 37%; overall $P < .001$; Fig 3A). The separation of the HR group was consistently seen in MCL Younger (Fig 3B) and MCL Elderly (Fig 3C) and for TTF

  

**Table 2.** Cox Regression Analyses for Overall Survival and Time to Treatment Failure Including MIPI Factors or MIPI Score

| Variable | Pooled Trials | | | | MCL Younger | | | MCL Elderly | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Beta | Hazard Ratio | 95% CI | *P* | Hazard Ratio | 95% CI | *P* | Hazard Ratio | 95% CI | *P* |
| OS, MIPI factors | | | | | | | | | | |
| Age, years (+1) | 0.04581 | 1.05 | 1.03 to 1.06 | < .001 | 1.03 | 1.003 to 1.06 | .030 | 1.07 | 1.04 to 1.10 | < .001 |
| ECOG PS (2 *v* 0/1) | 0.6585 | 1.93 | 1.35 to 2.76 | < .001 | 1.51 | 0.76 to 3.03 | .24 | 2.13 | 1.40 to 3.25 | < .001 |
| LDH/ULN (10-fold*) | 2.262 | 9.60 | 5.65 to 16.3 | < .001 | 7.91 | 3.08 to 20.3 | < .001 | 11.1 | 5.81 to 21.2 | < .001 |
| WBC count, $10^6$/L (10-fold*) | 0.6162 | 1.85 | 1.46 to 2.35 | < .001 | 2.32 | 1.54 to 3.50 | < .001 | 1.74 | 1.30 to 2.32 | < .001 |
| OS, MIPI score | | | | | | | | | | |
| MIPI score (+1) | 1.0226 | 2.78 | 2.41 to 3.21 | < .001 | 2.69† | 2.09 to 3.45 | < .001 | 2.74† | 2.23 to 3.37 | < .001 |
| TTF, MIPI factors | | | | | | | | | | |
| Age, years (+1) | 0.03797 | 1.04 | 1.03 to 1.05 | < .001 | 1.03 | 1.01 to 1.05 | .010 | 1.05 | 1.03 to 1.08 | < .001 |
| ECOG PS (2 *v* 0/1) | 0.7243 | 2.06 | 1.51 to 2.81 | < .001 | 1.52 | 0.83 to 2.79 | .17 | 2.44 | 1.69 to 3.52 | < .001 |
| LDH/ULN (10-fold*) | 1.782 | 5.94 | 3.74 to 9.42 | < .001 | 3.71 | 1.68 to 8.20 | .001 | 8.70 | 4.95 to 15.3 | < .001 |
| WBC count, $10^6$/L (10-fold*) | 0.3346 | 1.40 | 1.13 to 1.72 | .0017 | 1.49 | 1.04 to 2.14 | .028 | 1.42 | 1.09 to 1.83 | .008 |
| TTF, MIPI score | | | | | | | | | | |
| MIPI score (+1) | 0.7998 | 2.23 | 1.97 to 2.52 | < .001 | 1.89‡ | 1.53 to 2.32 | < .001 | 2.35‡ | 1.96 to 2.82 | < .001 |

Abbreviations: Beta, regression coefficient; ECOG PS, Eastern Cooperative Oncology Group performance status[9]; LDH, lactate dehydrogenase; MCL, mantle-cell lymphoma; MIPI, MCL International Prognostic Index; OS, overall survival; TTF, time to treatment failure; ULN, upper limit of normal.
*LDH/ULN and WBC count per $10^{-6}$L were $\log_{10}$-transformed for Cox regression.
†$P = .84$ for interaction of MIPI score and trial cohort with regard to OS.
‡$P = .11$ for interaction of MIPI score and trial cohort with regard to TTF.

(Data Supplement). The c-index for OS of MIPI-b was 0.70 as compared with 0.68 for MIPI, and for TTF 0.67 as compared with 0.65 (Data Supplement).

### *s-MIPI*

s-MIPI classified 32% of patients as LR, 36% as IR, and 32% as HR (Table 1). The concordance with the MIPI was high (weighted kappa, 0.79; 95% CI, 0.76 to 0.82) with 18% discordant cases (none between LR and HR, 9% between LR and IR, and 9% between IR and HR). s-MIPI discriminated three prognostic groups with 5-year OS rates of 81%, 63%, and 35%, respectively ($P < .001$; Data Supplement) and hazard ratios 2.0 (1.5 to 2.8) for IR versus LR and 2.5 (2.0 to 3.2) for HR versus IR. Five-year TTF rates according to s-MIPI were 59%, 36%, and 23%, respectively ($P < .001$; Data Supplement). MIPI and s-MIPI had comparable c-index for OS (0.683 and 0.680) and TTF (0.654 and 0.647; Data Supplement).

## DISCUSSION

The results of the present study confirm the prognostic value of MIPI on a large independent patient cohort. In adult patients of all ages with advanced stage, newly diagnosed MCL treated according to recognized standards, the MIPI discriminated three groups of LR, IR, and HR, with markedly different 5-year OS rates of 83%, 63%, and 34%, respectively. According to each higher risk group, the hazard of death was more than doubled. All four patient characteristics determining

**Table 3.** Complete Remission and Overall Response Rates after Induction According to the Mantle-Cell Lymphoma International Prognostic Index in Pooled Trials and Separate Trial Cohorts

| Response | LR | | IR | | HR | | *P* |
|---|---|---|---|---|---|---|---|
| | n/N | % | n/N | % | n/N | % | |
| Pooled trials | | | | | | | |
| CR/CRu/PR | 289/307 | 94 | 264/295 | 89 | 239/319 | 75 | < .001 |
| CR/CRu | 152/307 | 50 | 150/295 | 51 | 128/319 | 40 | .0137 |
| CR | 105/307 | 34 | 105/295 | 36 | 84/319 | 26 | .0263 |
| MCL Younger | | | | | | | |
| CR/CRu/PR | 254/270 | 94 | 94/105 | 90 | 52/63 | 83 | .0141 |
| CR/CRu | 129/270 | 48 | 47/105 | 45 | 24/63 | 38 | .38 |
| CR | 90/270 | 33 | 25/105 | 24 | 14/63 | 22 | .08 |
| MCL Elderly | | | | | | | |
| CR/CRu/PR | 35/37 | 95 | 170/190 | 89 | 187/256 | 73 | < .001 |
| CR/CRu | 23/37 | 62 | 103/190 | 54 | 104/256 | 41 | .0031 |
| CR | 15/37 | 41 | 80/190 | 42 | 70/256 | 27 | .0033 |

NOTE. Response was evaluated according to 1999 consensus criteria.[11]
Abbreviations: CR, complete remission; CRu, unconfirmed complete remission; HR, high risk; IR, intermediate risk; LR, low risk; MCL, mantle-cell lymphoma; PR, partial remission.

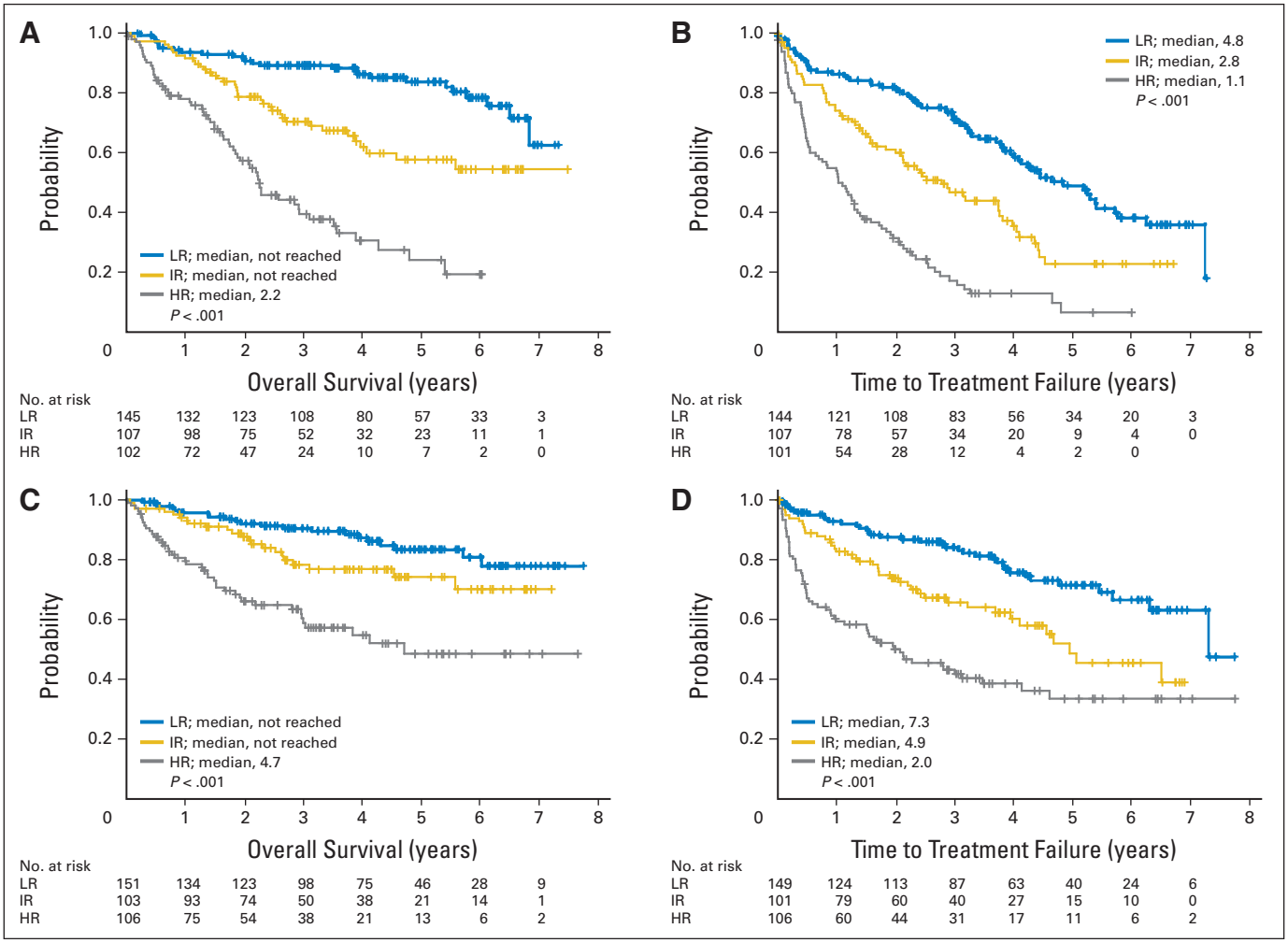


**Fig 2.** Overall survival (OS) and time to treatment failure (TTF) according to the Mantle-Cell Lymphoma (MCL) International Prognostic Index (MIPI) in pooled trials stratified by treatment (pretrials standards or superior treatment arms). (A) OS of patients treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by either autologous stem-cell transplantation (ASCT; MCL Younger) or interferon-alfa maintenance (MCL Elderly) in remission (26, 37, and 60 events, respectively). (B) TTF of patients treated with R-CHOP followed by either ASCT (MCL Younger) or interferon-alfa maintenance (MCL Elderly) in remission (69, 65, and 84 events, respectively). (C) OS of patients treated with either R-CHOP/rituximab plus dexamethasone, cisplatin, and cytarabine (R-DHAP) followed by ASCT in remission (MCL Younger) or R-CHOP followed by rituximab maintenance in remission (MCL Elderly; 21, 22, and 42 events, respectively). (D) TTF of patients treated with either R-CHOP/R-DHAP followed by ASCT in remission (MCL Younger) or R-CHOP followed by rituximab maintenance in remission (MCL Elderly; 36, 40, and 63 events, respectively). The interaction *P* values of MIPI risk groups and treatment groups were .21 for OS and .62 for TTF. HR, high risk; IR, intermediate risk; LR, low risk.

the MIPI, age, ECOG PS, LDH, and WBC count were confirmed as independent prognostic factors for OS.

Since its publication in 2008, the prognostic value of MIPI has been explored by many others.[16-41] However, most of these studies were performed on rather small cohorts of fewer than 100 patients with fewer than 40 events. So far, only three of 25 reports did not confirm the prognostic relevance of MIPI for OS, but these had low event numbers or short follow-up.[25,33,39]

In addition to OS, the primary end point for the development of the MIPI,[5] we showed the prognostic impact of MIPI and all MIPI factors with respect to the more disease-specific end point TTF. Furthermore, MIPI groups revealed different CIR of nonresponse or progression. Of 15 evaluations of MIPI with respect to progression-free survival,[16,17,19,22,23,25,27-31,33-35,41] its prognostic value was not confirmed in three cases,[22,25,33] of which only one had a reasonable statistical power.[22]

Current treatment recommendations for MCL[42] depend on patient age, including high-dose therapy for younger and fit patients and excluding it for older patients. Although the MIPI was developed for patients of all ages and age is a MIPI factor, we now confirmed its prognostic value separately for younger patients suitable for intensified treatment and older patients. In younger patients, the independent prognostic impact of ECOG PS could not be confirmed. Because only 4% of MCL Younger patients had ECOG PS 2, this did not limit the validity of MIPI in younger patients. By definition, the LR group in MCL Younger was relatively large (61%). In fact, this group revealed a favorable prognosis with 5-year OS of > 80% and 5-year TTF of 60%, whereas IR and HR groups revealed a substantially worse outcome. These results are in line with external validations from others performed on patients who received high-dose treatment.[16,19,23,27,39] We will further investigate the prognostic impact of MIPI in the superior study arm of MCL Younger, including high-dose cytarabine before ASCT.

  

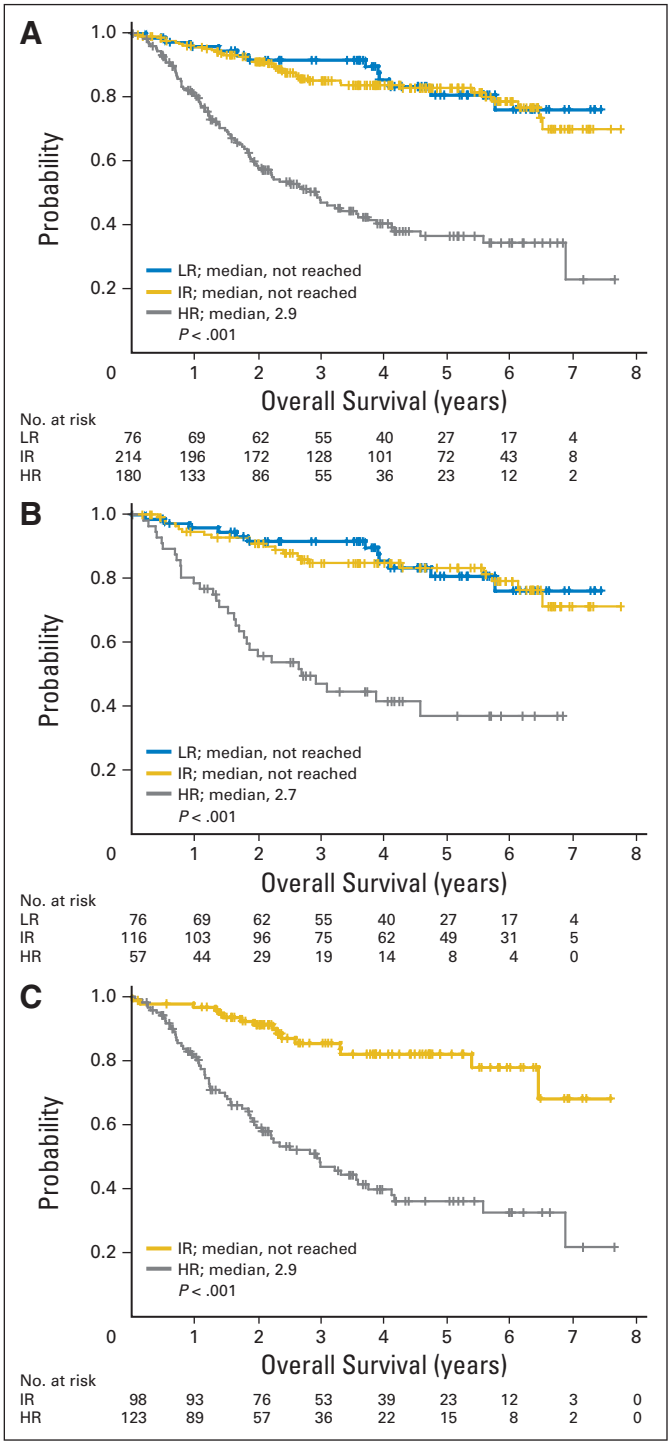


**Fig 3.** Overall survival according to biologic Mantle-Cell Lymphoma (MCL) International Prognostic Index (MIPI-b) in pooled trials (A), MCL Younger (B), and MCL Elderly (C). Patients with MIPI-b score below 5.70 were classified as low risk (LR), patients with an MIPI-b score ≥ 5.70 but < 6.50 as intermediate risk (IR), and patients with an MIPI score of 6.50 or higher as high risk (HR).[5] The MIPI-b score was calculated as 0.03535 × age (years) + 0.6978 (if ECOG PS > 1, otherwise 0) + 1.367 × $\log_{10}$(LDH/ULN) + 0.9393 × $\log_{10}$(WBC count per $10^{-6}$L) + 0.02142 × Ki-67 index (%). No patient of MCL Elderly was classified as LR according to MIPI-b. The numbers of events were 12, 37, and 95 for LR, IR, and HR patients of pooled trials, respectively (A), 12, 21, 31 for LR, IR, and HR patients of MCL Younger, respectively (B), and 16 and 64 for IR and HR patients of MCL Elderly, respectively (C). ECOG PS, Eastern Cooperative Oncology Group performance status; Ki-67, protein encoded by the *MKI76* gene; LDH, lactate dehydrogenase; ULN, upper limit of normal.

In MCL Elderly MIPI, MIPI score and MIPI factors were of high prognostic relevance. Only few MCL Elderly patients were classified as LR, reflecting the advanced age in this trial, and outcome was not clearly separated from the IR group. This might be explained by patient selection, because patients between 60 and 65 years suitable for high-dose treatment should enter MCL Younger and thus, older patients with more favorable risk profile were not included in MCL Elderly. Consequently, the application of MIPI to age groups younger than or older than 60 years confirmed the discrimination of survival curves with no interaction between age group and MIPI risk group. Therefore, our results reveal that MIPI is valid for risk stratification in older patients. For research purposes (eg, for stratified randomization), an adaptation of cutoff values for the MIPI score in patient cohorts of higher age may be useful. The only published evaluation focusing on older patients[28] confirmed the prognostic value of MIPI for progression-free survival and OS.

We confirmed the high concordance of s-MIPI and MIPI along with comparable prognostic capacity. Accordingly, we recommend the use of s-MIPI in clinical practice. For research purposes, especially when adjusting for prognostic factors, the continuous MIPI score or the continuous MIPI factors should be used in order not to unnecessarily lose substantial statistical power.[43]

Tumor cell proliferation, as measured by counting Ki-67 positive tumor cells according to the published guideline,[10] was confirmed as prognostic factor independent of MIPI. Furthermore, although MIPI-b did not separate LR and IR groups, and the HR group revealed substantially worse outcome, the addition of Ki-67 to MIPI allowed a strong discrimination between patients with good and dismal prognosis. MIPI-b had already been shown to be prognostic for progression-free survival[44] and OS[32,44] in conventionally treated patients[44] and a population based cohort,[32] and to separate an HR group with younger patients treated with high-dose cytarabine and ASCT.[23] Importantly, to allow an application in the routine care setting, pathologists should determine the Ki-67 index according to the published guideline,[10] because the quantitative evaluation of Ki-67 may be hampered by substantial interindividual variation.[10,45]

In contrast to the previous trials from which MIPI was derived, the trials used here for validation included 5% of patients with stage II. Advanced stage did not reveal additional prognostic relevance to the MIPI factors ($P = .95$ for OS; $P > .99$ for TTF). However, the number of patients with limited stage was too small to evaluate the prognostic value of MIPI in this subset. Other studies that included 2% to 17% of stage II patients have confirmed the MIPI.[23,24,26,28,32,39] Whether MIPI is valid for the small number of patients with stage I MCL who might be treated with combined modality treatment or radiation only remains an open question.

In the cohort of MIPI development, not all patients had received immunochemotherapy, and not all patients suitable for high-dose treatment were assigned to receive autologous stem-cell transplantation. The presented results reveal the validity of MIPI especially for patients treated according to current guidelines.[42] MIPI has been developed and validated in medically fit patients who tolerate moderate to intensive treatment strategies. In addition, candidate patients for deferred initial therapy[46] by the discretion of the treating physician were only occasionally included in the trials. On the other hand, two reports have confirmed the MIPI on population-based cohorts,[31,32,40] including > 20% of patients with an ECOG PS of 2 to 4. One report[40] revealed that comorbidity factors were not independently prognostic






129.125.61.1

of MIPI, and the authors explained this observation by the fact that performance status was included in the MIPI, which partly reflects the presence of comorbidity. This underlines the importance to assess the performance status in both clinical routine and research.

In conclusion, we confirm the validity of MIPI as a prognostic instrument on a large MCL patient cohort treated according to current standards within randomized trials. Based on current recommendations,[42] MIPI should be applied in routine clinical care. It may further be used in research to assess and compare the risk profiles of MCL patient cohorts, to adjust for imbalanced risk profiles in epidemiological studies, to allow risk-stratified randomization in clinical trials, and to provide a basis to establish new clinical or biologic prognostic factors. Finally, MIPI might be considered as an integral part in the development of individualized risk-adapted treatment strategies to further improve outcome in MCL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** None **Consultant or Advisory Role:** Jan Walewski, Roche (C); Christian H. Geisler, Roche (C), Janssen (C), Celgene (C), Boehringer Ingelheim (C), GlaxoSmithKline (C) **Stock Ownership:** None **Honoraria:** Jan Walewski, Roche **Research Funding:** Jan Walewski, Roche **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

## AUTHOR CONTRIBUTIONS

**Conception and design:** Eva Hoster, Martin H. Dreyling, Michael Unterhalt
**Collection and assembly of data:** All authors
**Data analysis and interpretation:** Eva Hoster, Martin H. Dreyling, Michael Unterhalt
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

## REFERENCES


1. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361-1392, 1994
2. Swerdlow S, Campo E, Harris NL, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (International Agency for Research on Cancer, Lyon, France). Geneva, Switzerland, WHO, 2008
3. Zhou Y, Wang H, Fang W, et al: Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 113:791-798, 2008
4. Herrmann A, Hoster E, Zwingers T, et al: Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol 27:511-518, 2009
5. Hoster E, Dreyling M, Klapper W, et al: A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 111:558-565, 2008
6. Hermine O, Hoster E, Walewski J, et al: Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). ASH Annual Meeting Abstracts 116:110, 2010
7. Hermine O, Hoster E, Walewski J, et al: Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared to 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Final analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). ASH Annual Meeting Abstracts 120:151, 2012
8. Kluin-Nelemans HC, Hoster E, Hermine O, et al: Treatment of older patients with mantle-cell lymphoma. N Engl J Med 367:520-531, 2012
9. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982
10. Klapper W, Hoster E, Determann O, et al: Ki-67 as a prognostic marker in mantle cell lymphoma: Consensus guidelines of the pathology panel of the European MCL Network. J Hematop 2:103-111, 2009
11. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17:1244, 1999
12. Ahnn S, Anderson SJ: Sample size determination for comparing more than two survival distributions. Stat Med 14:2273-2282, 1995
13. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988
14. Harrell FE, Califf RM, Pryor DB, et al: Evaluating the yield of medical tests. JAMA 247:2543-2546, 1982
15. Cohen J: Weighted kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 70:213-220, 1968
16. Budde LE, Guthrie KA, Till BG, et al: Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. J Clin Oncol 29:3023-3029, 2011
17. Chang JE, Peterson C, Choi S, et al: VcR-CVAD induction chemotherapy followed by maintenance rituximab in mantle cell lymphoma: A Wisconsin Oncology Network study. Br J Haematol 155:190-197, 2011
18. Chiappella A, Puccini B, Ferrero S, et al: Retrospective analysis of 206 mantle cell lymphoma patients at diagnosis: Mantle Cell International Prognostic Index (MIPI) is a good predictor of death event in patients treated either with rituximab-chemotherapy or rituximab-high-dose-chemotherapy. ASH Annual Meeting Abstracts 116:1784, 2010
19. Damon LE, Johnson JL, Niedzwiecki D, et al: Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 27:6101-6108, 2009
20. Dong HJ, Zhou LT, Fang C, et al: TP53 mutation is not an independent prognostic factor in patients with mantle cell lymphoma at advanced stage. Med Oncol 29:2166-2173, 2011
21. Dunleavy K, Neelapu SS, Kwak LW, et al: Association of idiotype vaccine-induced T-cell response with improved survival and time-to-next treatment (TTNT) in untreated mantle cell lymphoma (MCL). J Clin Oncol 30, 2012 (suppl; abstr 2528)
22. Eve HE, Gambell J, Smith P, et al: The Simplified Mantle-Cell Lymphoma International Prognostic Index predicts overall survival but not progression-free survival in patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide +/− rituximab: Results of a randomized phase II trial. Leuk Lymphoma 50:1709-1711, 2009
23. Geisler CH, Kolstad A, Laurell A, et al: The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 115:1530-1533, 2010
24. Gressin R, Caulet-Maugendre S, Deconinck E, et al: Evaluation of the (R)VAD+C regimen for the treatment of newly diagnosed mantle cell lymphoma: Combined results of two prospective phase II trials from the French GOELAMS group. Haematologica 95:1350-1357, 2011
25. Mato AR, Zielonka T, Feldman T, et al: The association between the Mantle Cell Lymphoma International Prognostic Index (MIPI) and survival in patients treated with rituximab-HCVAD (RHCVAD) alternating with rituximab-methotrexate-AraC (R-MTX-AraC). J Clin Oncol 28, 2010 (suppl; abstr 8092)
26. Merli F, Luminari S, Ilariucci F, et al: Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of


  

patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 156:346-353, 2012

**27.** Peterlin P, Leux C, Gastinne T, et al: Is ASCT with TBI superior to ASCT without TBI in mantle cell lymphoma patients? Transplantation 94:295-301, 2012

**28.** Raty R, Honkanen T, Jantunen E, et al: Prolonged immunochemotherapy with rituximab, cytarabine and fludarabine added to cyclophosphamide, doxorubicin, vincristine and prednisolone and followed by rituximab maintenance in untreated elderly patients with mantle cell lymphoma: A prospective study by the Finnish Lymphoma Group. Leuk Lymphoma 53:1920-1928, 2012

**29.** Romaguera JE, Fayad LE, Feng L, et al: Ten-year follow-up after intense chemoimmunotherapy with rituximab-HyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol 150:200-208, 2010

**30.** Ruan J, Martin P, Furman RR, et al: Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. J Clin Oncol 29:690-697, 2011

**31.** Salek D, Vasova I, Pytlik R, et al: Mantle cell lymphoma international prognostic score is valid and confirmed in unselected cohort of patients treated in rituximab era. ASH Annual Meeting Abstracts 112:3745, 2008

**32.** Salek D, Vesela P, Boudova L, et al: Retrospective analysis of 235 unselected patients with mantle cell lymphoma confirms prognostic relevance of Mantle Cell Lymphoma International Prognostic Index and Ki-67 in the era of rituximab: Long-term data from the Czech Lymphoma Project Database. Leuk Lymphoma [epub ahead of print on August 13, 2013]

**33.** Schaffel R, Hedvat CV, Teruya-Feldstein J, et al: Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. Ann Oncol 21:133-139, 2010

**34.** Shah BD, Cultrera JL, Sokol L, et al: Evaluation of the Mantle Cell Lymphoma International Prognostic Index (MIPI) as an indicator of overall survival, progression free survival, survival from relapse. ASH Annual Meeting Abstracts 116:5082, 2010

**35.** Smith SD, Hsi E, Bolwell B, et al: Validation of the Mantle Cell Lymphoma International Prognostic Index: A single-center retrospective analysis. Am J Hematol 85:454-456, 2010

**36.** Spurgeon SE, Pindyck T, Okada C, et al: Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. Leuk Lymphoma 52:1488-1494, 2011

**37.** Terol MJ, Teruel AI, Amat P, et al: Validation of the new prognostic index (MIPI) in mantle cell lymphoma: A single institution experience. Ann Oncol 19, 2008 (abstr 439)

**38.** Todorovic M, Balint B, Andjelic B, et al: Outcome prediction of advanced mantle cell lymphoma by international prognostic index versus different mantle cell lymphoma indexes: One institution study. Med Oncol 29:2212-2219, 2011

**39.** van 't Veer MB, de Jong D, MacKenzie M, et al: High-dose Ara-C and beam with autograft rescue in R-CHOP responsive mantle cell lymphoma patients. Br J Haematol 144:524-530, 2009

**40.** van de Schans SA, Janssen-Heijnen ML, Nijziel MR, et al: Validation, revision and extension of the Mantle Cell Lymphoma International Prognostic Index in a population-based setting. Haematologica 95:1503-1509, 2010

**41.** Ying ZT, Zheng W, Wang XP, et al: The clinical features, therapeutic responses, and prognosis of the patients with mantle cell lymphoma. Chin J Cancer 31:348-353, 2012

**42.** Dreyling M, Thieblemont C, Gallamini A, et al: ESMO Consensus conferences: Guidelines on malignant lymphoma—Part 2: Marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol 24:857-877, 2013

**43.** Royston P, Altman DG, Sauerbrei W: Dichotomizing continuous predictors in multiple regression: A bad idea. Stat Med 25:127-141, 2006

**44.** Chiappella A, Frairia C, Puccini B, et al: Mantle Cell Lymphoma International Prognostic Index (MIPI) and Biological-MIPI are better predictors of the outcome of mantle cell lymphoma (MCL) patients than IPI: A retrospective analysis. Haematologica 94:395, 2009 (abstr 0981)

**45.** de Jong D, Rosenwald A, Chhanabhai M, et al: Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: Validation of tissue microarray as a prerequisite for broad clinical applications: A study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 25:805-812, 2007

**46.** Martin P, Chadburn A, Christos P, et al: Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 27:1209-1213, 2009



 