Mantle cell lymphoma (MCL) comprises less than 10% of all cases of non-Hodgkin lymphoma and has heterogeneous clinical behavior ranging from indolent to very aggressive. The disease is characterized by the presence of t(11;14) and frequently presents at an advanced stage with a male predominance and median age of 64.\(^1\) There is currently no standard of care for patients with newly diagnosed MCL, although many fit patients are considered for intensive, Ara-C–containing, induction therapy followed by autologous stem cell transplantation (ASCT). This approach has resulted in a median time to treatment failure of up to 9 years in studies such as the recently reported MCL Younger study, and similar impressive results have been reported in other studies incorporating Ara-C–containing induction regimens with ASCT.\(^2\)\(^-\)\(^5\) In addition, currently available novel therapies and those still under investigation have markedly improved outcomes for patients with relapsed disease, resulting in prolonged overall survival (OS) for most patients with MCL, including those who cannot undergo ASCT in first remission.\(^6\)\(^-\)\(^11\) However, despite recent advances, most patients with MCL will ultimately die of their disease, and very few patients are cured outside of an allogeneic stem cell transplant (alloSCT).\(^12\) This review summarizes the currently available data regarding identification of indolent compared with aggressive disease, the role of ASCT in first remission, and the appropriate scenarios in which to use maintenance therapies.

Differentiating Between Aggressive and Less Aggressive MCL

Risk Stratification in MCL

Identification of low-risk disease and consideration of a watchful waiting approach. Although most patients with MCL will initiate therapy at the time of diagnosis, a subset of patients with indolent disease can be safely observed (Fig. 1). Martin et al first described a cohort of deferred patients at Cornell, where 31 patients who delayed treatment of at least 3 months could be safely monitored for a median of 12 months (range, 4-128 months) without a negative impact on OS.\(^13\) In this series, patients with a good performance status, lack of B-symptoms, and normal lactate dehydrogenase (LDH) have been associated with deferred therapy in some series. Finally, patients with early-stage disease and those with a leukemic
presentation (i.e., non-nodal with disease primarily limited to the peripheral blood) are also more likely to be observed.17 Interestingly, the MCL IPI (MIPI) has not been associated with selection of deferred therapy in any of the previously reported series, suggesting that this index may not adequately identify the subset of patients with indolent disease who are candidates for this approach. Patients with high-risk MIPI have been safely observed in all previously reported series.

A national cohort analysis from the National Cancer Database has also evaluated the role of deferred therapy throughout the United States.18 In this series, 492 of 8,029 (6%) patients received deferred therapy with a median time to treatment of 121 days (range, 91–1,152), and deferred therapy was associated with an improved OS (hazard ratio [HR] 0.79;) in this larger cohort. In a multivariable model, lack of B-symptoms was the strongest variable associated with receipt of deferred therapy, while extranodal presentation, Hispanic race, and residence outside of the Midwest or Southern regions were also associated with deferred therapy.

In the absence of randomized, prospective studies evaluating the role of deferred therapy, it appears that patients without symptoms, with low tumor burden, and without high-risk pathologic features can be safely observed, often for several years. In addition to the clinical and pathologic features mentioned above, SOX11 expression by immunohistochemistry (IHC) has been evaluated for its potential to identify low-risk, indolent cases. In a review of SOX11 IHC expression from the Nordic group for patients enrolled on the Nordic MCL 2 and 3 protocols, the high-expression group had a 10-year OS of 69% and patients with SOX11HIGH disease had improved OS in a multivariable model.19 A population-based series of 173 cases included 160 patients with SOX11 expression by IHC, and the median OS was 3.2 years for patients with SOX11-positive disease compared with 1.5 years for those with SOX11-negative disease.20 However, additional series have suggested that patients with SOX11-negative disease may in fact be predisposed to a leukemic, non-nodal presentation and indolent disease behavior, and this is reflected in the updated World Health Organization criteria, which identify leukemic, non-nodal MCL as a distinct entity that is SOX11-negative.21 Although its use in the right clinical scenario can provide useful prognostic information, SOX11 expression alone should not be used to identify indolent compared with aggressive disease without considering the clinical situation in a particular patient.

Prospective identification of high-risk patients and aggressive disease. Early identification of high-risk patients may allow providers to pursue alternative therapies and consider enrollment on clinical trials. Current approaches to identification of high-risk patients include MIPI risk score, Ki67 proliferative index, cytogenetics/fluorescent in situ hybridization, identification of genomic aberrations, and/or evaluation of gene expression profiling. Unfortunately, outcomes for patients with identified high-risk features remain poor, even with currently available Ara-C–containing induction, consolidation, and maintenance approaches.22,23

Although patients with low- and intermediate-risk MIPI scores have improved outcomes with currently available therapies, patients with high-risk MIPI scores enrolled in the European MCL Younger and MCL Elderly studies had a median OS of less than 3 years in a pooled analysis, and the median OS for high-risk patients in the MCL Younger cohort alone was only 3.8 years (Table 1).22 The median OS rates for the low- and intermediate-risk subsets were not reached in either study. The impact of MIPI has also been evaluated for the Nordic MCL2 study, in which the low-risk patients have a median OS not reached after 15 years of follow-up, the intermediate-risk patients have a median OS of 11 years, and the high-risk patients have a median OS of 4 years.24 Similar findings have been described by Damon et al with CALGB S9909, in which 67% of patients with high-risk MIPI died within the median follow-up of 4.7 years.5

**KEY POINTS**

- The MIPI integrates four clinical parameters with the Ki-67 proliferation index to identify patients with low- and high-risk disease.
- The best outcomes for younger patients with MCL have been achieved by incorporating high-dose Ara-C into induction therapy, followed by ASCT.
- AlloSCT strategies are most appropriate in the relapsed MCL setting.
- In older patients with MCL, maintenance rituximab has proven benefit after R-CHOP induction therapy, but its role after BR is controversial.
- In younger patients with MCL, maintenance rituximab administered after ASCT improves OS.
Ki67 proliferative index and pretreatment cytogenetic assessments have been evaluated alone and in combination with MIPI to better define high-risk subgroups. Work by Katzenberger et al and Hsi et al identified Ki67 as a marker of disease activity although the optimal cutoff for high-versus low-risk disease was not described.\textsuperscript{28,29} In recent years, 30% positivity has been frequently accepted as a cutoff for high-compared with low-Ki67 expression.\textsuperscript{30,31} Hoster and colleagues have evaluated the role of Ki67 in conjunction with MIPI in patients treated on the MCL Younger and MCL Elderly studies and identified a significantly worse 5-year OS of 41% for patients with Ki67 30% or greater when compared with patients with Ki67 less than 30%, whose 5-year OS was 73% to 75%.\textsuperscript{32} The impact of Ki67 was independent of MIPI risk score, and in a new model (MIPI-c) combining Ki67 and MIPI, patients were divided into four groups ranging from low risk (5-year OS: 85%) to high risk (5-year OS: 17%). In this analysis, blastoid growth identified pathologically was not prognostic for OS or progression-free survival (PFS) when Ki67 was included in a multivariable model.

Pretreatment cytogenetics has been used frequently in many hematologic malignancies to aid in risk stratification and therapy selection. In MCL, initial descriptions of outcomes for patients with a complex karyotype suggested inferior survival.\textsuperscript{33,34} A single-center study conducted at The Ohio State University of 80 patients with untreated MCL found that 32 patients (41% of the cohort) had a complex karyotype (defined as ≥ 3 chromosomal abnormalities) identified in involved bone marrow samples.\textsuperscript{35} Patients with a complex karyotype in this series were more likely to have an elevated leukocyte count, increased LDH, splenomegaly, and be high-risk by MIPI. Two-year OS for the complex karyotype group was 58% compared with 85% for the non-complex group. However, in this analysis, the presence of a complex karyotype was not predictive of OS independent of MIPI and other clinical variables. Sarkozy et al evaluated the role of cytogenetics in a series of 125 patients from France, where nodal tissue, bone marrow, or peripheral blood were used for cytogenetic evaluation.\textsuperscript{36} Fifty-nine percent of patients had a complex karyotype, and these patients were more likely to have a shortened time to initial therapy and an inferior OS in a multivariable model (HR 2.37); independent of high-risk MIPI score. This series also evaluated the prognostic impact of specific cytogenetic abnormalities, but none of the identified recurrent abnormalities were independently associated with OS. A larger cohort of patients with MCL from five centers evaluated the role of cytogenetics in untreated MCL and confirmed an association of a complex karyotype with inferior OS (median 4.5 years vs. 11.6 years for noncomplex karyotype). A multivariable model for OS confirmed that complex karyotype and elevated LDH were independently associated with decreased OS, while MIPI risk group was not.\textsuperscript{37}

Attempts to integrate prognostic markers into more comprehensive models have been challenging. Hoster and colleagues have combined Ki67 with MIPI to form the biologic MIPI (MIPI-b) and the MIPI-c.\textsuperscript{32} However, additional pathologic features in this series, such as blastoid variant histology, were not independently associated with outcome. Staton et al presented the results of a multicenter analysis of 92 patients with untreated MCL who had pretreatment Ki67, MIPI, and cytogenetics reports available for review.\textsuperscript{33} Within this series, a multivariable model indicated that Ki67 greater than 30% and complex karyotype were both independently associated with inferior PFS, while MIPI risk score was not. As a result, assessing the relative contribution of each described prognostic marker remains elusive, and many current projects are limited by modest sample sizes and heterogeneously treated patient populations. However, a number of currently available prognostic markers reliably identify high-risk patients, many of whom do not respond optimally to currently available therapy, and these patients should be considered for investigational therapies when available.

Table 1. Estimated Survival for Patients With MCL Based on MIPI Risk Group

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoster et al, 2008\textsuperscript{37}</td>
<td>409</td>
<td>5-year OS: 60%</td>
<td>Median 51 months</td>
<td>Median 29 months</td>
</tr>
<tr>
<td>Hoster et al, 2014\textsuperscript{42}</td>
<td>958</td>
<td>5-year OS: 83%</td>
<td>5-year OS: 63%</td>
<td>5-year OS: 34%</td>
</tr>
<tr>
<td>Budde et al, 2011\textsuperscript{26}</td>
<td>118</td>
<td>2.5-year OS: 93%</td>
<td>2.5-year OS: 60%</td>
<td>2.5-year OS: 32%</td>
</tr>
<tr>
<td>Eskelund et al, 2016\textsuperscript{24}</td>
<td>157</td>
<td>Median NR</td>
<td>Median 11 years</td>
<td>Median 4 years</td>
</tr>
<tr>
<td>Chihara et al, 2015\textsuperscript{22}</td>
<td>501</td>
<td>5-year OS: 74%</td>
<td>5-year OS: 70%</td>
<td>5-year OS: 35%</td>
</tr>
</tbody>
</table>

Abbreviation: MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; NR, not reached.

Novel approaches to risk stratification. Currently available approaches to identification of high-risk patients adequately identify patients at risk for early progression, but alternative methods are needed to better understand the biology of high-risk disease and to aid in the development of targeted therapies. Next-generation sequencing and assessment of gene expression offers the potential benefit of more specific identification of risk factors and potential therapeutic targets. Several projects have identified recurrent mutations in MCL, including ATM, CCND1, MLL2, WHSC1, TP53, NOTCH1, and others that occur at a lower frequency.\textsuperscript{18,39} In two larger series that included 56\textsuperscript{38} and 29\textsuperscript{39} patients, there were limited clinical data associated with the presence of the mutations. However, additional projects have identified specific mutations or alterations associated with high-risk disease behavior, including NOTCH1,\textsuperscript{40} CDKN2A,\textsuperscript{41} and TP53.\textsuperscript{41}

Prior attempts to characterize a proliferative signature in MCL through gene expression profiling have also successfully identified high-versus low-risk patients.\textsuperscript{42} However, this
assay historically required fresh tissue, making its use limited to centers equipped to perform these analyses in real time. As a result, assessment of proliferation by Ki67 has been used as a surrogate. In recent years, investigators with the Lymphoma/Leukemia Molecular Profiling Project have reliably assessed gene expression using extracted RNA from formalin-fixed, paraffin-embedded archival tissue to identify cell-of-origin in diffuse large B-cell lymphoma.43 Using this same technology, Scott and colleagues developed a 35-gene panel to identify three risk groups of patients with MCL, where high-risk patients have a median OS of 1.1 years and low-risk patients have a median OS of 8.6 years.44 This association remained significant (p < .05) when controlling for Ki67 proliferative index as well as MIPI risk score. This assay is prognostic but does not currently guide therapy selection. However, the ability to perform genomic assessments on preserved tissues may provide physicians with better tools to use when counseling patients and selecting therapies in the future.

**UNDERSTANDING WHO SHOULD RECEIVE A HEMATOPOIETIC CELL TRANSPLANT FOR MCL**

Patients requiring therapy are evaluated based on their ability to tolerate a stem cell transplant as most guidelines include an up-front ASCT as part of therapy.45 Besides biologic factors about the disease, the patient must be physiologically fit for high-dose therapy, ASCT, and possible complications associated with the conditioning regimen. Institutional limits to a minimum cardiovascular function, pulmonary reserve, and renal function are required for this procedure, and physiologic age and comorbidity index are increasingly being used to determine eligibility for transplant.46 The source of stem cells is another important factor in determining eligibility of transplantation. For ASCT, it requires the patient’s bone marrow is healthy enough for mobilization of stem cells, and for alloSCT, there needs to be a suitable donor (i.e., sibling, matched unrelated donor, cord blood, or a haplo-identical donor).

**Up-Front Therapies Including ASCT**

Initial attempts to treat MCL with regimens similar to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) produced inadequate results with most patients relapsing within 2 to 3 years.47,48 Improved responses were noted when rituximab was combined with various chemotherapy regimens including fludarabine, cyclophosphamide, and rituximab (FCR)49 and CHOP50 without significantly affecting time to treatment failure or OS. Following this, multiple aggressive approaches were developed to improve the outcome of younger patients with MCL as listed in Table 2. These studies typically exclude elderly frail patients most include patients with stage II to IV MCL who are considered transplant eligible. ASCT is performed only in patients with chemotherapy-sensitive disease.

One approach pioneered at The University of Texas MD Anderson Cancer Center consisted of alternating cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone with high-dose Arc-C and methotrexate (hyper-CVAD) and produced a response rate of 93% in previously untreated patients.58 Responding patients were taken to ASCT and experienced an impressive 3-year OS of 92% and event-free survival (EFS) of 72%. However, significant toxicity was noted. A phase II study of 97 patients treated with four cycles of rituximab and hyper-CVAD (R-hyper-CVAD) without ASCT resulted in a 3-year OS of 82%, with 64% of patients still in remission.51 A 15-year follow-up of this patient cohort shows that the median failure-free survival is 4.8 years and median OS is 10 years, with a plateau for FFS at 10 years. Toxicity consisted of myelodysplastic syndrome/acute myeloid leukemia of 6.2% at 10 years.59 Gruppo Italiano Studio Linfomi and Southwest Oncology Group have evaluated this regimen in a multicenter setting but found the toxicity to be too high even though outcomes were promising.52,53

Major groups in Europe have developed approaches to incorporate ASCT in up-front therapy. Dexamethasone, cisplatin, and high-dose Ara-C (DHAP) and then R-DHAP was added to CHOP/R-CHOP–based regimens to improve up-front response rates so that more patients could move to ASCT.3,60 A randomized trial between up-front ASCT after induction compared with interferon (IFN)-alpha confirmed higher response rates after ASCT and an improved EFS of 39 months compared with 17 months with IFN.54 Effect on OS was not demonstrated with the short follow-up. A dose-intensified Maxi-CHOP regimen with rituximab and high-dose Ara-C followed by ASCT55 (Nordic 2) has reported the best outcome to date with a median OS of 12.7 and PFS of 8.2 years.55 The European MCL Network (MCL Younger) has shown that the use of high-dose Ara-C in the up-front treatment of MCL with ASCT results in deeper remissions as indicated by negative minimal residual disease (MRD) status by nested polymerase chain reaction as well as increased PFS.2 In this study, 497 patients were randomly assigned to differing induction arms and ASCT where the experimental arm contained higher doses of Ara-C (14 mg/m² compared with 800 mg/m²) as part of DHAP as well as the conditioning regimen of ASCT. Complete responses (CRs) were higher in the Ara-C group (95% vs. 55%), but the objective response rate (ORR) was the same after ASCT in both arms. MRD negativity after induction was higher in the Ara-C group (79% vs. 47%) in the peripheral blood, and this difference was maintained in the bone marrow even after ASCT. At a median follow-up of 6.1 years, time to treatment failure was 9.1 years in the Ara-C group compared with 3.9 years, and OS was 76% at 5 years compared with 69% in the control group. The toxicity of multiagent chemotherapy has prompted investigators to evaluate other regimens that can still incorporate high-dose Ara-C. Armand et al47 evaluated 23 patients with MCL with three cycles of bendamustine plus rituximab (BR) followed by three cycles of high-dose Ara-C and rituximab followed by ASCT. Follow-up is short but the results are promising, as MRD-negative status was reached in 96% of cases after induction. Similarly, the LyMa trial is evaluating four cycles of R-DHAP prior to ASCT, reserving R-CHOP therapy only for patients who have a partial response to R-DHAP.56 Upcoming
TABLE 2. Studies of Aggressive Induction Regimens Including ASCT

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Planned Consolidation ASCT</th>
<th>Median Follow-up</th>
<th>Median CR</th>
<th>Median OS</th>
<th>Median DFS</th>
<th>TRM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP vs. CHOP</td>
<td>Lenz et al, 2005&lt;sup&gt;50&lt;/sup&gt;</td>
<td>122</td>
<td>Yes, for younger patients</td>
<td>34% vs. 7%</td>
<td>TTF 21 months vs. 14 months; NS</td>
<td>No diff. in OS and PFS</td>
<td>Rituximab improved initial response rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-hyper-CVAD with alternating MTX/Ara-C 6-8 cycles</td>
<td>Romaguera et al, 2005&lt;sup&gt;51&lt;/sup&gt;</td>
<td>97</td>
<td>No</td>
<td>15 years</td>
<td>87</td>
<td>82%; median OS is 4.8 years</td>
<td>64%; median FFS 8.8 years</td>
<td>5 died of toxicity; 4 developed MDS/AML; TRM 8%</td>
<td></td>
</tr>
<tr>
<td>R-hyper-CVAD x 4</td>
<td>Merli et al, 2012&lt;sup&gt;52&lt;/sup&gt;</td>
<td>60</td>
<td>Yes, only if PR</td>
<td>46 months</td>
<td>72</td>
<td>Median OS 73% at 5 years</td>
<td>5-year PFS 61%</td>
<td>Only 22% completed 4 cycles; 3 patients died; TRM 6.5%</td>
<td></td>
</tr>
<tr>
<td>R-hyper-CVAD x 8</td>
<td>Bernstein et al, 2013&lt;sup&gt;53&lt;/sup&gt;</td>
<td>49</td>
<td>No</td>
<td>4.8 years</td>
<td>55</td>
<td>6.8 years, 86%</td>
<td>Median PFS 4.8 years; 5.5 years if &lt; age 55</td>
<td>39% did not complete due to toxicity; TRM 2%</td>
<td></td>
</tr>
<tr>
<td>CHOP + R x 3 + R-DHAP x 3 (multi-center)</td>
<td>Delarue et al, 2013&lt;sup&gt;54&lt;/sup&gt;</td>
<td>60</td>
<td>Yes, in responding patients; TBI-based or BEAM</td>
<td>67 months</td>
<td>96; CR 12% after R-CHOP; 83% at 3 years vs. 77%</td>
<td>Median EFS 83 months; 5-year OS 75%</td>
<td>1.5%; secondary tumors 18%</td>
<td>Addition of rituximab improved EFS</td>
<td></td>
</tr>
<tr>
<td>CHOP or CHOP + R</td>
<td>Dreyling et al, 2005&lt;sup&gt;55&lt;/sup&gt;</td>
<td>122</td>
<td>Up-front randomization of IFN-alpha or ASCT; TBI based</td>
<td>After R-CHOP 35%; after ASCT 81%</td>
<td>5 years, 75%</td>
<td>Median EFS 83 months; 5-year OS 75%</td>
<td>0</td>
<td>Randomized trial that showed the efficacy of up-front ASCT for MCL</td>
<td></td>
</tr>
<tr>
<td>R-Maxi CHOP + HD Ara-C</td>
<td>Geisler et al, 2012&lt;sup&gt;56&lt;/sup&gt;</td>
<td>160</td>
<td>ASCT; BEAM/BEAC</td>
<td>6.5 years</td>
<td>Median OS 10 years</td>
<td>Median EFS 7.4 years</td>
<td>Late relapses after 5 years</td>
<td>MRD evaluation and preemptive rituximab therapy offered to eligible patients</td>
<td></td>
</tr>
<tr>
<td>R-CHOP x 6 + DexaBEAM + ASCT (TBI + Ara-C + Mel)</td>
<td>Hermine et al, 2013&lt;sup&gt;57&lt;/sup&gt;</td>
<td>497</td>
<td>Yes</td>
<td>6.1 years</td>
<td>95% in Ara-C vs. 55%</td>
<td>5 yr. OS 76% in Ara-C group vs. 69%</td>
<td>TTF 9.1 years in Ara-C group vs. 3.9 years</td>
<td>4%</td>
<td>MRD negativity after induction was higher in the Ara-C group 79% vs. 47%; MRD negativity strongest prognostic factor</td>
</tr>
<tr>
<td>R-DHAP x 4 + ASCT maintenance rituximab vs. observation after transplant</td>
<td>Le Gouill et al, 2016&lt;sup&gt;58&lt;/sup&gt;</td>
<td>299</td>
<td>Yes; if CR, ASCT; PR, R-CHOP x 4 ASCT</td>
<td>29.3 months</td>
<td>3 years 83%; no difference in 2 arms</td>
<td>3-year PFS 74%; 2-year EFS 93% in maintenance arm vs. 81%</td>
<td>Omission of anthracycline; rituximab maintenance improves EFS and OS</td>
<td></td>
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</tbody>
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Continued
trials are likely to incorporate more targeted agents, such as ibritumomab, in the up-front regimens challenging the paradigms listed above.

There is no consensus on conditioning regimens for ASCT. Earlier studies used total body irradiation (TBI)-based regimens and a benefit in MCL was suggested by a retrospective analysis (PFS after 4 years: 71% vs. 0%, \( p < 0.0001 \); OS 89% vs. 60%, \( p = 0.07 \))\(^{61}\) with some indication that it may lead to improve outcomes, but this approach has been associated with an increased incidence of second malignancies and other toxicities, and the field has moved away from it. Single agents \(^{90}\)Y-ibritumomab-tiuxetan and \(^{131}\)I-tositumomab have shown activity both in up-front therapy of MCL and in relapsed MCL and are an attractive means of delivering radiation to the malignant cells without the toxicity of radiation therapy.\(^{62,63}\) Both agents had been safely combined with high-dose chemotherapy as conditioning for ASCT with no increased toxicity.\(^{54,65}\) In the Nordic MCL-3,\(^{66}\) \(^{90}\)Y-ibritumomab-tiuxetan was used in an attempt to overcome the inherent chemotherapy resistance of a suboptimal response to up-front chemoimmunotherapy treated on the MCL-2 regimen. The ORR was 97%, and 4-year OS and PFS was 78% and 71%, respectively, similar to patients in the Nordic MCL-2 group. Use of \(^{90}\)Y-ibritumomab-tiuxetan in patients as consolidation after hyper-CVAD has demonstrated unacceptable toxicity with 20% of the patients dying because of second malignancies.\(^{67}\)

**Predictors of response after ASCT.** Despite high response rates, the approaches described above are challenging and there is significant risk of toxicity and second malignancies. In addition, 10% to 30% of patients undergoing aggressive induction never make it to ASCT either because of chemotherapy resistance or complications such as infections or cardiac events. A careful evaluation of some of the larger series has pointed to a few prognostic factors that can be used to predict outcomes particularly after ASCT, including MIPI/MIPI-b, MRD status, and PET scan response prior to transplant. The Nordic 2 trial demonstrated that the MIPI-b was a prognostic factor with 70% of low intermediate patients alive at 10 years compared with only 23% with a high MIPI-b.\(^{55}\) In the MCL-3 trial, a positive PET before transplant as well as MRD-positive status predicted for a poor outcome.\(^{66}\) Pott et al\(^{68}\) reported on 27 patients post-ASCT who underwent MRD evaluation. Median PFS was 92 months if MRD-negative compared with 21 months in patients with MRD-positive disease. This was further confirmed in the larger European MCL Network study where 56% of patients achieved MRD after initial chemoimmunotherapy, and this predicted for a prolonged response duration at 2 years: 94% if MRD-negative compared with 71% if MRD-positive. ASCT increased the proportion of MRD from 55% to 72%, and a sustained MRD negativity predicted for improved outcome at 2 years (100% vs. 65% for MRD-positive). Thus, patients with poor prognostic factors, including positive MRD after induction therapy, may benefit from alternative approaches for long-term outcome.

**Relapsed Setting.** ASCT in MCL is less effective when offered to patients in the relapsed disease with median PFS of 1 to 2 years. Outcomes of patients undergoing ASCT was better in first complete remission when compared with transplants performed later in the disease, even when chemotherapy sensitivity was demonstrated.\(^{58,69,70}\) The use of radio-immunotherapy (RIT) in conditioning regimens may be a way to improve outcomes, and this approach has been reported.\(^{64,71}\) In a non-randomized trial of RIT-containing conditioning regimens compared with conventional regimens for patients with chemoresistant disease from a single institution, the use of RIT was associated with improvements in both PFS and OS following ASCT.

**Allogeneic Stem Cell Transplant for MCL.** In spite of improved outcomes seen in MCL with the above described approaches, nearly all patients with MCL will relapse. The median OS of patients who relapse after ASCT is reported at 19 months,\(^{72}\) though this may change with the approval of newer targeted agents. AlloSCT remains an option for suitable patients and can lead to long-term remissions and potential cures. The use of an alloSCT in relapsed lymphoma elicits a graft-versus-lymphoma effect allowing for long-term remissions, albeit at a risk of graft-versus-host disease, infections, and organ dysfunction that can lead to a risk of transplant-related mortality. The use of a reduced intensity-conditioning regimen relies on graft-versus-lymphoma effect and reduced acute toxicity allowing its use in elderly and frail patients or in patients who have failed an earlier myeloablative ASCT.
Early case reports of alloSCT in MCL performed in the 1990s demonstrated long-term remission in patients with chemo-refractory disease.\textsuperscript{73,74} Several centers have reported the outcome of patients with MCL undergoing alloSCT as listed in Table 3 over the past 15 years. There is variability in patient selection, conditioning regimens, and supportive measures. The longest follow-up is 5 years with reported PFS of approximately 30% and OS of up to 50% in some of the newer series. Of note, even patients with refractory disease prior to transplant can achieve long-term remission. Hamadani et al\textsuperscript{80} reported a 5-year survival of 25% in patients with refractory disease; however, transplant-related mortality was one of the highest in this series. Magnusson et al\textsuperscript{81} have reported that even patients with PET-positive disease could undergo salvage alloSCT. The 5-year disease-free survival and relapse rates after allogeneic hematopoietic cell transplantation were 34% and 25% for all patients and 40% and 33% for residual disease recipients, respectively, suggesting that active disease at the time of allograft does not preclude long-term remissions in advanced MCL.

EBMT Registry data show that patients who relapsed more than 1 year after ASCT and had a salvage alloSCT had a better outcome with a 5-year OS of 60%.\textsuperscript{77} There appears to be no difference between myeloablative and reduced intensity-conditioning regimens in terms of outcomes even though there are no studies of direct comparisons. The use of donor lymphocyte infusion to induce remissions in patients with relapsed disease after an alloSCT indicate that there is a graft-versus-lymphoma effect in MCL. The use of RIT with \textsuperscript{90}Y-ibritumomab tiuxetan as part of reduced intensity-conditioning conditioning has been evaluated by Fred Hutchinson Cancer Research Center with no clear advantage to its use.

The use of alloSCT has been studied in first remission in comparison with ASCT as reported by Fenske et al,\textsuperscript{83} and even though the 5-year relapse was lower in the allo-SCT arm (15% vs. 32%, respectively), there was increased transplant-related mortality of 25% at 1 year after the alloSCT resulting in no difference in the 5-year PFS and OS of both arms. Evens et al used an intensive induction regimen of high-dose Ara-C and randomly assigned young patients to sibling alloSCT or ASCT, but only four patients completed the alloSCT.\textsuperscript{85} A German group reported on alloSCT in first remission compared with the relapsed setting with no difference between the two arms, thus failing to demonstrate an advantage for an earlier alloSCT.\textsuperscript{83} In the series from Cruz et al, there were 21 patients who had an alloSCT in first complete remission and showed a 5-year PFS and OS of 80% but with a transplant-related mortality of 19%.\textsuperscript{80} Hence, at this time, it cannot be recommended that an alloSCT be performed in first complete remission except in clinical trials.

**IS THERE A ROLE FOR MAINTENANCE THERAPY IN MCL?**

Maintenance therapy with rituximab has been tested in a variety of settings, with most, but not all, studies indicating clinical benefit. Two randomized clinical trials have demonstrated an OS benefit when maintenance rituximab was used as part of initial management of MCL. Many areas of uncertainty remain, however, including the optimal rituximab dose and schedule and the impact of different induction strategies maintenance rituximab efficacy. For example, one study suggested no benefit for maintenance rituximab after a BR induction. This section will review the data around maintenance rituximab in MCL and consider other maintenance strategies that may find their way into practice.

**Early Studies of Maintenance Rituximab in MCL**

Given the significant durable PFS benefit, maintenance rituximab has demonstrated in follicular lymphoma, it was natural to speculate that maintenance rituximab might be beneficial in MCL.\textsuperscript{86,87} MCL was considered an incurable entity with a relatively poor prognosis. Response rates to initial therapy were high, but remissions tended to be short lived. Finally, there was a paucity of good options for management in the relapsed setting. Hence, any strategy that could prolong remission was attractive. The first trial to evaluate maintenance rituximab formally came from the Swiss Group for Clinical Cancer Research.\textsuperscript{88} Both untreated and previously treated patients were enrolled and assigned to receive four weekly doses of rituximab. Patients without progression were then randomly assigned to receive maintenance rituximab (four more doses over 8 months) or no further therapy. There was no obvious benefit for the maintenance rituximab using this strategy. The following year, the German Low-Grade Lymphoma Study Group published a study demonstrating a significant (\(p = .049\)) response duration benefit for maintenance rituximab in relapsed MCL.\textsuperscript{89} The first study of maintenance rituximab focusing on the front-line setting came from the Wisconsin Oncology Network, who reported on a single-arm, phase II study evaluating maintenance rituximab for 2 years after a chemoimmunotherapy induction.\textsuperscript{90} The 3-year PFS of 50% was substantially better than historical controls using R-CHOP-like induction therapy and strongly suggested a benefit for maintenance rituximab. Patients only achieving a partial remission to the induction did not appear to benefit from maintenance rituximab, suggesting a complete remission may be necessary for maintenance rituximab to provide additional benefit. No worrisome safety signals were noted. Long-term follow-up of this cohort revealed that 30% remained progression-free beyond 5 years, again suggesting a potential for long-term benefit after maintenance rituximab.\textsuperscript{91} A follow-up study by the Wisconsin Oncology Network tested the use of maintenance rituximab for 5 years after a chemoimmunotherapy induction.\textsuperscript{92} The patient population was similar to the previous trial: untreated MCL of any age, requiring therapy. In this follow-up study, the 3-year PFS was 63%, and 50% of patients remained progression-free after 5 years.\textsuperscript{93} In fact, no relapses beyond 5 years have been observed in this cohort, again suggesting significant benefit for maintenance rituximab. However, 5 years of maintenance rituximab did appear to translate into more infectious complications,
with only 20% of the group able to complete all 5 years of the planned treatment. The Eastern Cooperative Oncology Group confirmed these promising results in E1405.94 In this trial, after a moderately intensive induction strategy, patients could be assigned to either maintenance rituximab or ASCT at the investigators’ discretion. Despite the fact that the patients assigned to maintenance rituximab were generally older with higher MIPI scores, maintenance rituximab performed as well as ASCT for PFS and OS. However, until 2012, the use of maintenance rituximab remained sporadic as definitive evidence of benefit was lacking.

**Evidence supporting maintenance rituximab in older patients with MCL.** The use of maintenance rituximab in MCL began to gain widespread acceptance with the landmark publication by the European MCL Consortium.95 Patients with MCL age 60 and older were randomly assigned to six cycles of FCR or to eight cycles of R-CHOP. Responding patients underwent a second randomization to receive maintenance rituximab or IFN-alpha, each given until progression. Treatment until progression was a unique feature as all previous trials of maintenance rituximab in MCL had selected arbitrary stopping points of 8 months, 2 years, or 5 years. Analysis of the trial is complicated because of the use of two different induction strategies and the 2 × 2 factorial design. When combining the two induction arms and comparing maintenance rituximab to IFN-alpha, there was a significant (p < .001) improvement in remission duration, favoring maintenance rituximab with a 45% reduction in the risk of progression or death. At 4 years, 58% of the patients in the maintenance rituximab arm were still in remission, compared with 29% of those receiving IFN-alpha.

When analyzing the impact of maintenance rituximab according to induction therapy received, one can see that the induction therapy matters. The remission duration benefit of maintenance rituximab was limited to the patients assigned to R-CHOP and was not apparent in patients assigned to R-CHOP and was not apparent in patients assigned to maintenance rituximab or IFN-alpha, each given until progression. Treatment until progression was a unique feature as all previous trials of maintenance rituximab in MCL had selected arbitrary stopping points of 8 months, 2 years, or 5 years. Analysis of the trial is complicated because of the use of two different induction strategies and the 2 × 2 factorial design. When combining the two induction arms and comparing maintenance rituximab to IFN-alpha, there was a significant (p < .001) improvement in remission duration, favoring maintenance rituximab with a 45% reduction in the risk of progression or death. At 4 years, 58% of the patients in the maintenance rituximab arm were still in remission, compared with 29% of those receiving IFN-alpha.

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assigned to FCR. There is precedent for such a differential effect following induction. In E1496, a frontline follicular lymphoma trial, patients were randomly assigned to receive cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy or FC chemotherapy, with patients whose disease did not progress being randomly assigned to maintenance rituximab for 2 years or observation. A substantial remission duration benefit was observed after CVP chemotherapy, but no benefit was seen after FC chemotherapy. Why maintenance rituximab would be beneficial after one type of induction therapy and not another is not precisely known. It is possible that the profoundly immunosuppressive effects of fludarabine-based therapy negate critical effector cell functions necessary for optimal rituximab effectiveness.

The impact of maintenance rituximab on the patients treated with R-CHOP was strong enough to translate into an OS benefit. Based on these striking results, maintenance rituximab gained rapid and widespread adoption in the frontline management of older patients with MCL. An important caveat, however, centers on current induction strategies and whether maintenance rituximab confers the same benefit irrespective of the induction. Two small randomized clinical trials have indicated that BR is a superior induction strategy compared with R-CHOP. As a result, BR as the induction strategy has gained widespread adoption in North America and Europe. Whether maintenance rituximab still confers benefit in patients receiving BR induction was the subject of a recent analysis presented at the 2016 ASCO Annual Meeting. The frontline StiL NHL7-2008 study in indolent lymphoma was conducted in Germany and Austria and included a subgroup of patients with MCL. These 168 patients were considered ineligible for high-dose therapy and their median age was 71. They received six cycles of BR induction therapy, and patients whose disease responded were randomly assigned to maintenance rituximab for 2 years or to observation. Just 122 patients ultimately were randomly assigned—60 to observation and 62 to maintenance. The median PFS was 54.7 months for observation compared with 72.3 months for maintenance, but this difference was not statistically different (HR 0.71; p = .223). These results are not yet published, but the presentation did garner significant attention and has caused many to question whether maintenance rituximab after BR induction is warranted.

Evidence supporting maintenance rituximab in younger patients with MCL. In general, outcomes with initial therapy are much better for younger patients with MCL than they are for older patients with MCL. Younger patients typically have lower-risk disease, as measured by the MIPI. They are also more suitable candidates for intensive induction strategies, which tend to produce more durable remissions. One would predict it would be more difficult to show benefit from any sort of maintenance strategy in this population. The first publication to suggest benefit for maintenance rituximab in young patients with MCL who received an intensive frontline treatment came from investigators at the Fred Hutchinson Cancer Research Center. In this retrospective study, the investigators examined a cohort of consecutive patients with MCL that underwent ASCT for MCL and then evaluated outcomes according to whether the patient received maintenance rituximab after ASCT (50 patients) or did not (107 patients). The decision on whether to administer maintenance rituximab was made by the treating physician, and a variety of schedules were used. With a median follow-up of 5 years, maintenance rituximab was associated with an improved PFS (HR 0.44; p = .007) and OS (HR 0.46; p = .03). Grade 4 neutropenia was more common in the maintenance rituximab group (34% vs. 18%, respectively) but this did not translate into increased mortality. Although provocative, this retrospective analysis could not be viewed as definitive as there were some key differences in the two populations. Patients receiving maintenance rituximab were more likely to have received high-dose Ara-C during induction and more likely to be in CR at the time of ASCT. The investigators acknowledge that the strategy of maintenance rituximab after ASCT would require confirmation in a prospective randomized controlled trial.

Such confirmation was presented at the 2016 American Society of Hematology Meeting, where the final results of the LyMa trial (NCT00921414) were presented. The trial was limited to patients with MCL age 65 and younger, and all patients received induction therapy with four cycles of R-DHAP followed by ASCT using rituximab, carbustine, etoposide, Ara-C, and melphalan (R-BEAM) conditioning. Randomization to maintenance rituximab, consisting of a single dose every 2 months for 3 years or to observation, occurred post-ASCT. The median age was 57, and over half of the patients were low risk by MIPI, which is typical for this patient population. Two hundred ninety-nine patients were enrolled, and 240 patients were randomly selected (120 in each arm). The primary endpoint was EFS with events defined as progression, death, or severe infection after randomization. The final analysis demonstrated that maintenance rituximab after ASCT significantly prolonged EFS (78.9% vs. 61.4%, respectively) at 4 years (HR = 0.46; p = .0016). Maintenance rituximab also prolonged OS at 4 years (88.7% vs. 81.4%, respectively; HR = 0.5; p = .045). There was no difference in the rate of severe infections between maintenance rituximab and observation. Given the OS advantage noted, these results strongly support the use of maintenance rituximab after ASCT in younger patients with MCL. Randomized clinical trials evaluating maintenance rituximab are summarized in Table 4.

Other Maintenance Strategies Under Investigation

Ongoing studies yet to be analyzed, but which could impact the standard of care, are summarized in Table 5. Lenalidomide has demonstrated single-agent activity in MCL and, for mechanistic reasons, has been combined with rituximab in both induction and maintenance strategies, with promising early results. The U.S. Intergroup trial E1411 (NCT01415752) is focused on older patients with MCL and
is testing 2 years of single-agent rituximab against 2 years of rituximab plus lenalidomide. The primary endpoint is PFS. This trial completed enrollment in September of 2016 (372 patients) and is expected to read out for the primary endpoint in 2019. The Bruton tyrosine kinase inhibitor ibrutinib has impressive single-agent activity in MCL, and the SHINE trial (NCT01776840) has enrolled 520 older patients with MCL. Following induction therapy with BR or BR plus ibrutinib, patients receive either maintenance rituximab for 2 years or maintenance rituximab for 2 years plus ibrutinib administered indefinitely. The results of SHINE are expected in 2018 or 2019. Ibrutinib is also being tested in combination with intensive strategies as part of the European MCL Consortium TRIANGLE study (NCT02858258). This three-arm study will compare ASCT alone, ibrutinib maintenance alone, and ASCT plus ibrutinib maintenance. Finally, the U.S. Intergroup trial EA4151 will also compare maintenance rituximab with ASCT plus maintenance rituximab in patients who have achieved an MRD-negative CR to induction therapy. This trial is scheduled to begin enrollment in 2017.

### CONCLUSION

Maintenance rituximab has been shown to improve OS in both older and younger patients with MCL. However, important questions remain regarding the optimal dose and schedule. Should maintenance be administered for 2 years, 3 years, or indefinitely? In addition, it remains unclear whether the induction strategy impacts the efficacy of maintenance. In the trial supporting maintenance rituximab in older patients, the benefit was seen only after R-CHOP induction. However, a small study evaluating maintenance rituximab for 2 years after a bendamustine-based induction did not find any benefit. More study of maintenance rituximab after BR induction is warranted so that remaining discrepancies can be resolved. Maintenance rituximab for 3 years after ASCT in younger patients with MCL was shown to favorably impact OS and represents a new standard of care. Ongoing trials in Europe (TRIANGLE) and in North America (EA4151) will test whether alternative maintenance strategies can replace ASCT or whether such strategies should be an adjunct to ASCT.

### TABLE 5. Trials in Progress Testing Novel Maintenance Strategies in MCL

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Population</th>
<th>Status</th>
<th>No. of Patients</th>
<th>Maintenance Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1411 (NCT01415752)</td>
<td>Older MCL; frontline regimen</td>
<td>Fully enrolled</td>
<td>372</td>
<td>Rituximab vs. rituximab + lenalidomide</td>
</tr>
<tr>
<td>SHINE (NCT01776840)</td>
<td>Older MCL; frontline regimen</td>
<td>Fully enrolled</td>
<td>520</td>
<td>Rituximab vs. rituximab + ibrutinib</td>
</tr>
<tr>
<td>TRIANGLE (NCT02858258)</td>
<td>Younger MCL; frontline regimen</td>
<td>Enrollment started 2016</td>
<td>870</td>
<td>ASCT vs. ASCT + ibrutinib vs. ibrutinib</td>
</tr>
<tr>
<td>EA4151 (NCT pending)</td>
<td>Younger MCL; frontline regimen</td>
<td>Enrollment to begin 2017</td>
<td>412</td>
<td>Rituximab vs. rituximab + ASCT in MRD negative first remission</td>
</tr>
</tbody>
</table>

Abbreviations: MCL, mantle cell lymphoma; ASCT, autologous stem cell transplantation; MRD, minimal residual disease.
References


