Non-Hodgkin’s Lymphomas

Version 2.2015

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Mantle Cell Lymphoma
MANT-1

**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - IHC panel: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, Ki-67
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular analysis to detect: antigen receptor gene rearrangements; CCND1 rearrangements
- Cytogenetics or FISH: t(11;14), t(14;18), CLL panel
- IHC for SOX11

**WORKUP**

**ESSENTIAL:**
- Physical exam: Attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Bone marrow biopsy ± aspirate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Hepatitis B testing if rituximab contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin
- Comprehensive metabolic panel
- LDH
- Bone marrow biopsy ± aspirate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Hepatitis B testing if rituximab contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Endoscopy/colonoscopy
- Neck CT
- Uric acid
- Discussion of fertility issues and sperm banking
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin
- PET-CT scan

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*aTypical immunophenotype: CD5+, CD20+, CD43+, CD23-/-, cyclin D1+, CD10-/-, CD21, BCL2, BCL6, Ki-67. Note: Some cases of MCL may be CD5- or CD23+. If the diagnosis is suspected, cyclin D1 staining or FISH for t(11;14) should be done. There are rare cases of CCND1- MCL (<5%) with an otherwise typical immunophenotype.*

*bSee Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).*

*cKi-67 proliferation fraction of <30% is associated with a more favorable prognosis. However, it is not used to guide treatment.*

*dHepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.*

*eEssential for confirmation of stage I-II disease. See Discussion for details.*

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**INDUCTION THERAPY**

**INITIAL RESPONSE**

**FOLLOW-UP**

**RELAPSE**

**SECOND-LINE THERAPY**

**Stage I, II** (localized presentation, extremely rare)

- Complete response
  - See Suggested Regimens (MANT-A) ± RT, or RT.

- Partial response or Progression
  - Prior treatment with RT alone
  - See Induction Therapy (MANT-3)

**Stage II bulky, III, IV**

- Prior treatment with chemotherapy ± RT

**FOLLOW-UP**

- Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated
  - Relapse

**RELAPSE**

- Prior treatment with RT alone
  - See Induction Therapy (MANT-3)

- Prior treatment with chemotherapy ± RT
  - See Induction Therapy (MANT-3)

**SECOND-LINE THERAPY**

- Clinical trial
  - or Second-line treatment
  - RT
  - See Suggested Regimens (MANT-A)

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See [Principles of Radiation Therapy (NHODG-D)]().


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See [Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C)].

Clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.
Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.

See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

Clinical trials of adjuvant therapy or for relapsed disease involving high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.


Consider second-line therapy to improve partial response.

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**Induction Therapy**

- **Aggressive therapy**
  - CALGB regimen (Treatment 1, 2, 2.5: rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]; Treatment 3: etoposide, cytarabine, rituximab; Treatment 4: carmustine, etoposide, cyclophosphamide/autologous stem cell rescue; Treatment 5: rituximab maintenance) (Treatment 2.5 is given if the pre-Treatment 3 bone marrow biopsy contains >15% MCL.)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine
  - Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)
  - Sequential RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide)

- **Less aggressive therapy**
  - Bendamustine + rituximab ± maintenance rituximab
  - VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
  - Cladribine + rituximab
  - CHOP + rituximab followed by consolidation with rituximab maintenance (375 mg/m2 every 8 wks until progression) (category 1 for maintenance)
  - Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y

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**First-line Consolidation**

- Clinical trial
- High-dose therapy with autologous stem cell rescue

**Second-line Therapy**

- Bendamustine ± rituximab
- Bortezomib ± rituximab
- Cladribine + rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
- FMR (fludarabine, mitoxantrone, rituximab)
- Ibrutinib
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab
- See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

**Second-line Consolidation**

- Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

**Consider prophylaxis for tumor lysis syndrome** (See NHODG-B)

**See monoclonal antibody and viral reactivation** (NHODG-B)

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SUGGESTED TREATMENT REGIMENS

References

Less aggressive therapy

Bendamustine + rituximab


Bendamustine + rituximab + maintenance rituximab


VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) alternating with rituximab + high-dose cytarabine


CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) + rituximab


Modified HyperCVAD with rituximab maintenance


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Continued on next page
First-line Consolidation

High-dose therapy with autologous stem cell rescue


Lenalidomide + rituximab

PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab

FCM (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

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Mantle Cell Lymphoma

Diagnosis

Mantle cell lymphoma (MCL) comprises about 6% of all newly diagnosed cases of NHL. MCL can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents. The diagnosis can be established by histological examination in combination with immunohistochemistry (IHC) with a profile consisting of CD5+, CD10-/-+, CD20+, CD23/-+, CD43+, and cyclin D1+. Some cases of MCL may be CD5- or CD23+. MCL is characterized by the reciprocal chromosomal translocation t(11;14), resulting in the overexpression of cyclin D1 and the diagnosis of MCL generally requires the expression of cyclin D1. However, cyclin D1-negative MCL cases with otherwise typical immunophenotype can be observed, though rare (<5% of cases). Recent gene expression profiling data suggest that cyclin D1 expression may not be required for the molecular signature of MCL; in these rare cases of MCL negative for cyclin D1 and t(11;14), over-expression of cyclin D2 or cyclin D3 may be observed. IHC for cyclin D2 or cyclin D3 is not helpful in establishing the diagnosis of cyclin D1-negative MCL as these proteins are also expressed in other B-cell malignancies. A recent study of cyclin D1-negative MCL showed rearrangements involving the CCND2 gene in 55% of cases, which was associated with high expression of cyclin D2 mRNA. Gene expression and miRNA profiling showed that the genomic signatures of cyclin D1-negative MCL cases were similar to those of cyclin D1-positive cases. Nuclear overexpression of the transcription factor SOX11 is observed in nearly all cases of MCL, regardless of cyclin D1 expression level, and may potentially aid in differentiating cyclin D1-negative MCL cases from other B-cell lymphomas. The pathologic features and clinical characteristics of cyclin D1-negative MCL appear to be similar to those of cyclin D1-positive cases. Thus, in the absence of data suggesting otherwise, cases of cyclin D1-negative MCL should not be managed differently than cyclin D1-positive cases.

Currently available reagents for IHC evaluation of cyclin D1 are robust and yield good staining; however, in some cases, molecular analysis of CCND1 rearrangements or cytogenetics or FISH for the translocation t(11;14), juxtaposing the cyclin D1 locus with the IgH locus, can be helpful for diagnosis. In certain cases, cytogenetics or FISH for t(14;18) and a FISH panel for chronic lymphocytic leukemia (CLL) may also be useful. In addition, Ki-67 should be included in the IHC panel for initial diagnostic workup. Ki-67 proliferation index of less than 30% has been associated with a more favorable prognosis. However, this should not be used to guide treatment decisions at this time.

In-Situ Involvement of Mantle Cell Lymphoma-like Cells of Unknown Significance (Mantle Cell Lymphoma “In Situ”)

The presence of MCL-like B-cells in the mantle zones of morphologically reactive lymph nodes (“MCL in situ”) has been described in several case reports (including in patients with lymphoid hyperplasia). Cases of “MCL in situ” have been characterized by preservation of the lymph node architecture and presence of cyclin D1-negative MCL cases with minimal expansion of the mantle zone (and with only minimal or no spread of cyclin D1-positive cells in the interfollicular area). More recently, an unusual case of “MCL in situ” was reported that showed a scattering of cyclin D1-positive cells in the germinal centers (but not the mantle zones) of a lymph node specimen retrospectively evaluated several years prior to the diagnosis of symptomatic MCL.

The occurrence of “MCL in situ” in studies of reactive lymph nodes was very rare. In an analysis of a consecutive series of unselected surgical samples of reactive lymph nodes from patients without a history
of lymphoma (n=131; 1292 samples), no cases of “MCL in situ” were identified. Development of overt MCL in patients found to have “MCL in situ” has been reported, although this appears to be very uncommon. The significance or potential for malignancy of “MCL in situ” in patients without known MCL remains uncertain. These cases appear to have a very indolent course with long-term survival even without treatment intervention. It is therefore important to distinguish cases of “MCL in situ” from cases of overt MCL with a mantle zone pattern. In patients with the former in whom overt MCL can be excluded based on a thorough evaluation (e.g., biopsy of additional suspicious nodes, physical examination, peripheral blood flow cytometry, CT scan of neck, chest, abdomen, and pelvis) close follow-up may still be warranted. Similar to “follicular lymphoma in situ”, the WHO classification recommends that a diagnosis of MCL not be made in such cases.

**Workup**

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. The initial workup for newly diagnosed MCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH). Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. Measurement of serum beta-2-microglobulin levels may also be useful in some circumstances. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. MCL is a systemic disease with frequent involvement of the bone marrow, gastrointestinal (GI) tract and may also present with a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Adequate trephine biopsy should be obtained for initial staging evaluation, with or without bone marrow aspiration. Chest, abdominal, and pelvic CT scans are routinely performed. PET-CT scan and CT scan of the neck may be helpful in selected cases. In patients with the blastic variant or for patients presenting with CNS symptoms, a lumbar puncture should be performed to evaluate the cerebral spinal fluid for potential disease involvement.

GI involvement has been reported in 15% to 30% of patients with MCL. In two prospective studies, the frequency of GI tract involvement in patients with MCL was higher than that reported in the literature. Salar et al reported upper or lower GI tract involvement in 92% of patients at diagnosis. In the study by Romaguera et al., MCL was histologically present in the lower and upper GI tract in 88% and 43% of patients, respectively. In this report, 26% of patients presented with GI symptoms at the time of diagnosis. Despite the high frequency of GI tract involvement (which was primarily observed at the microscopic level), the use of endoscopy with biopsies led to changes in clinical management in only 4% of patients. The NCCN Guidelines panel does not recommend endoscopy or colonoscopy as part of routine initial workup, but suggests that it may be useful in certain circumstances. However, endoscopic or colonoscopic evaluation of the GI tract is necessary for confirmation of stage I-II disease and for response assessment to initial therapy.

**Treatment Options based on Clinical Stage**

Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to the incurability of
disease with conventional chemotherapy and a more aggressive disease course.\textsuperscript{27}

\textit{Stage I-II}

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. In a retrospective analysis of patients with limited bulk, early-stage (stage IA or IIA) MCL (n=26), inclusion of RT with or without chemotherapy was associated with significantly improved progression-free survival (PFS) at 5 years (68\% vs. 11\%; \( P = .002 \)) and a trend towards improved overall survival (OS).\textsuperscript{28}

\textit{Stage II (bulky) and Stage III-IV}

Several regimens have shown significant activity in newly diagnosed patients with MCL, but none of these regimens are curative in patients with advanced disease.

In a database analysis from a single-center cohort (n=111), Martin et al reported that treatment with regimens including R-CHOP or R-CVP could yield survival outcomes similar to that achieved with more intensive approaches.\textsuperscript{29} The median OS from diagnosis was 85 months, and the 5-year OS rate was 66\%. Among patients with available data on treatment regimens (n=75), the majority (70\%) had received CHOP-like therapy with or without rituximab, with only 7\% having received more intensive first-line therapies (R-hyper-CVAD and/or high-dose therapy with autologous stem cell rescue [HDT/ASCR]).\textsuperscript{29}

However, a more recently published analysis from the NCCN Oncology Outcomes Database suggested that median PFS remained 3-4 years despite the use of aggressive regimens in patients with MCL (n=167).\textsuperscript{30} This analysis reported superior PFS outcomes with R-hyper-CVAD alone or with rituximab-containing regimens (e.g., R-CHOP) followed by HDT/ASCT, compared with R-CHOP alone, in the first-line setting for younger patients (<65 years of age) with MCL.\textsuperscript{30}

\textit{Aggressive First-Line Therapy}

Rituximab used in combination with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; alternating with high-dose methotrexate and cytarabine) [R-hyper-CVAD] has resulted in favorable PFS and OS outcomes.\textsuperscript{31-34}

In a phase II study in previously untreated patients with MCL (n=97), R-hyper-CVAD produced 3-year failure-free survival (FFS) and OS rates of 64\% and 82\%, respectively, with a median follow-up time of 40 months.\textsuperscript{31} After 10 years of follow-up, the median OS had not been reached and the median time to failure (TTF) was 4.6 years for all patients. Among patients 65 years or younger, the median OS had not been reached and the median TTF was 5.9 years. In the multivariate analysis pre-treatment serum levels of beta-2-microglobulin, IPI score and MIPI score were predictive of both OS and TTF.\textsuperscript{32} FFS and OS rates were 43\% and 60\%, respectively; among patients 65 years or younger, the corresponding survival rates were 52\% and 68\%, respectively.

In the Italian study (60 evaluable patients), R-hyper-CVAD resulted in an overall response rate of 83\% with a CR rate of 72\%. The 5-year PFS and OS rates were 61\% and 73\%, respectively.\textsuperscript{33} However, this regimen was associated with substantial toxicity.

In the SWOG 0213 study, R-hyper-CVAD induced CR/CRu in 58\% of previously untreated patients (age <70 years) with MCL (n=49).\textsuperscript{34} With a median follow-up of 4.8 years, the median PFS and OS was 4.8 years (5.5 years for those ≤ 65 years) and 6.8 years respectively. The 2-year PFS and OS rates were 63\% and 76\%, respectively.
Less Aggressive First-Line Therapy
In the earlier studies, the addition of rituximab to CHOP chemotherapy was associated with high response rates but did not translate to prolonged PFS or OS.\(^{35,36}\) A phase III randomized trial in the German Low Grade Lymphoma study group evaluated R CHOP versus CHOP alone in previously untreated patients (age ≤65 years) with advanced stage MCL (n=122).\(^{36}\) In this study, R CHOP was significantly superior to CHOP in terms of ORR (94% vs. 75%), CR rate (34% vs 7%) and median time to treatment failure (21 months vs. 14 months). However, no differences were observed between treatment arms for PFS or OS outcomes.\(^{36}\)

Other non-aggressive regimens have also been evaluated in clinical trials. The combination of bendamustine with rituximab (BR regimen) was investigated in a randomized phase III study of the StiL (Study Group Indolent Lymphomas), which compared BR versus R-CHOP as first-line therapy in patients with advanced follicular, indolent, and mantle cell lymphomas (514 evaluable patients; MCL histology comprised 18% of patients).\(^{37}\) The ORR was similar in both arms (93% with BR vs. 91% with R-CHOP), although the CR rate was significantly higher in the BR arm (40% vs. 30%; \(P = .021\)). With a median follow-up time of 45 months, the BR arm was associated with significantly longer median PFS (primary endpoint) compared with R-CHOP (69.5 months vs. 31.2 months; HR=0.58, 95% CI 0.44–0.74, \(P < .0001\)); however, OS outcomes were not significantly different between treatment arms. Among the subgroup of patients with MCL histology, median PFS was also significantly higher with BR compared with R-CHOP (35 months vs. 22 months; HR=0.49, 95% CI 0.28–0.79; \(P = .0044\)).\(^{37}\) The BR regimen was associated with less frequent serious adverse events (19% vs. 29%) and less grade 3-4 hematologic toxicities compared with R-CHOP. Grade 3-4 neutropenia was reported in 29% in the BR arm and 69% with R-CHOP. Peripheral neuropathy (all grades) was less frequent in the BR arm (7% vs. 29%). Infectious complications (all grades) were also less frequent with BR compared with R-CHOP (37% vs. 50%). Fatal sepsis occurred in 1 patient in the BR arm and 5 patients in the R-CHOP arm. The BR regimen was more frequently associated with skin toxicities (all grades) including erythema (16% vs. 9%) and allergic reactions (15% vs. 6%) compared with R-CHOP.\(^{37}\)

Although this phase III randomized trial showed superior PFS outcomes with the BR regimen compared with R-CHOP, there may be limitations given that data from more than half of the patients in this trial were censored prior to the minimum follow-up period.

The combination of bendamustine and rituximab with the addition of cytarabine was evaluated in a phase II study in older patients with MCL (age ≥ 65 years; not eligible for intensive regimens or HDT/ASCR).\(^{38}\) Among enrolled patients (n=40; median age 70 years), 50% were previously untreated, 93% had stage III/IV disease and 49% had high-risk MIPI scores. Patients with relapsed/refractory disease (n=20) had all previously received rituximab-containing therapies.\(^{38}\) Among previously untreated patients, the ORR was 100% and the 2-year PFS rate was 95%. Among relapsed/refractory patients, the ORR was 70% and the 2-year PFS was 70%. The most common grade 3 or 4 toxicities included transient thrombocytopenia (87%) and febrile neutropenia (12%).\(^{38}\)

Cladribine, alone or in combination with rituximab, has shown activity in patients with previously untreated MCL.\(^{39-41}\) In trials conducted by the North Central Cancer Treatment group, the ORR and median PFS for single agent cladribine were 81% (42% CR) and 14 months, respectively, for previously untreated patients (n=26); the combination of cladribine and rituximab as initial therapy (n=29) resulted in an ORR of 66% (52% CR) and median PFS of 12 months.\(^{39}\) In a small trial in
patients with previously untreated and pretreated MCL (n=12), cladribine alone induced an ORR of 58% (25% CR) with a median time to progression of 19 months.40 In a recent retrospective study in patients with previously untreated MCL (n=31), cladribine combined with rituximab yielded an ORR of 87% (61% CR/CRu) with a median PFS and OS of 37.5 months and 85 months, respectively.41 It should be noted that in this study, the majority of responding patients had received post-induction maintenance therapy with rituximab.

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL42-44 and is currently approved for this indication. A phase III randomized study evaluated the safety and efficacy of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs. R-CHOP in patients with newly diagnosed MCL who are not candidates for HDT/ASCR.45 In this study, 487 patients were randomized to R-CHOP (n = 244) or VR-CAP (n = 243). The majority of patients had stage IV disease (74%) and 54% of patients had an IPI ≥3. At a median follow-up of 40 months, median progression-free survival with VR-CAP was 24.7 months compared to 14.4 months for R-CHOP, which was statistically significant (P < .001). VR-CAP was also associated with improvements in median time to progression (30.5 vs 16.1 months; P < .001) and CR (CR + CRu) rate (48% vs. 41%).45 The median duration of response (CR + CRu) was 42 months and 18 months, respectively. The 4-year OS rate was higher with VR-CAP (64% vs. 54% for R-CHOP), but the benefit was not significant. The incidences of grade ≥3 adverse events, although slightly higher with VR-CAP (93% compared to 84% with R-CHOP), were manageable. Based on the results of this study, the FDA approved the use of bortezomib (in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone) for the initial treatment of patients with MCL. The NCCN Guidelines have included VR-CAP as an option for induction therapy for patients with newly diagnosed MCL (stage II-IV).

First-Line Consolidation Therapy
HDT/ASCR as first-line consolidation has demonstrated promising outcomes in a number of studies.46-52

In a prospective study of sequential frontline CHOP/DHAP followed by HDT/ASCR in patients with MCL (n=28; n=23 proceeded to transplant), the 3-year event-free survival (EFS) and OS rates were 83% and 90%, respectively.48 Median OS was not reached after a median follow-up of almost 48 months. In a randomized trial conducted by the European MCL Network, patients (age ≤65 years) with advanced stage MCL (n=122) in remission after CHOP-like chemotherapy were randomized to HDT/ASCR or maintenance with interferon alfa.49 In this study, HDT/ASCR was associated with a significantly longer median PFS compared with interferon alfa maintenance (39 months vs. 17 months; P=0.011) The 3-year OS rates were 83% and 77%, respectively, and were not significantly different between consolidation arms.49

In a study conducted by the MD Anderson Cancer Center, HDT/ASCR in patients with MCL (n=33) in first remission following treatment with hyper-CVAD resulted in 5-year disease-free survival and OS rates of 42% and 77%, respectively.47 In particular, the subgroup of patients with low serum beta-2 microglobulin levels appeared to benefit most, with a 5-year OS rate of 100% (compared with 22% for patients with elevated beta-2 microglobulin).47 In an analysis of long-term outcomes from patients with MCL treated at the MD Anderson Cancer Center (including the 33 patients reported in the earlier study above), the subgroup of patients treated primarily with hyper-CVAD (with or without rituximab) followed by HDT/ASCR in first remission (n=50) showed a median PFS of 42 months and a median OS of 93 months.51
In a small prospective study that evaluated R-hyper-CVAD followed by HDT/ASCR in patients with previously untreated MCL (n=13; 12 patients proceeded to transplant), the 3-year EFS and OS rate was 92% for both endpoints.\textsuperscript{50} These results with R-hyper-CVAD appear favorable relative to induction with R-CHOP.

In a phase II study that evaluated R-CHOP induction followed by HDT/ASCR in patients with previously untreated MCL (n=87; 61 patients proceeded to transplant), the 4-year failure-free survival and OS rates were 36% and 66%, respectively.\textsuperscript{52}

In another study, patients with MCL treated with hyper-CVAD or CHOP (with or without rituximab, in either regimen) followed by HDT/ASCR in first remission (n=36) had 3-year PFS and OS rates of 63% and 93%, respectively.\textsuperscript{53} Induction with hyper-CVAD resulted in a higher 3-year PFS rate compared with CHOP (81\% vs. 44\%), although the difference was not statistically significant. The 3-year OS rate was similar between induction regimens (94\% vs. 92\%, respectively).\textsuperscript{53} Disease status at transplant was the most significant factor affecting survival following HDT/ASCR.\textsuperscript{53,54} Patients in first remission (CR or PR) at the time of transplant had improved survival outcomes compared with those with relapsed or refractory disease. As mentioned above, among patients transplanted in first remission, hyper-CVAD (with or without rituximab) induction was associated with an improved PFS outcome compared with CHOP (with or without rituximab) in non-randomized studies.\textsuperscript{53}

Several different induction regimens incorporating rituximab in combination with dose intensified anthracycline-based\textsuperscript{16,55,56} or cladribine-based chemotherapy\textsuperscript{57,59} followed by HDT/ASCR have shown promising efficacy in relatively young newly diagnosed patients with MCL.

In the Nordic MCL trial, induction therapy with rituximab and dose intensified CHOP (maxi-CHOP) alternating with high-dose cytarabine resulted in an ORR and CR rate of 96\% and 54\%, respectively, in previously untreated patients (age ≤65 years) with MCL (n=160).\textsuperscript{55} Responding patients were eligible to proceed with HDT/ASCR. The 6-year PFS and OS rates were 66\% and 70\%, respectively, with no relapses occurring after a median follow up of approximately 4 years (at the time of the initial report).\textsuperscript{55} Further follow up from this study with a median observation time of 6.5 years showed median EFS of 7.4 years; median OS exceeded 10 years.\textsuperscript{60} Late relapses were reported in 6 patients, who experienced disease progression more than 5 years after the end of therapy. In the multivariate analysis from this study, the international MCL Prognostic Index (MIPI) and ki-67 expression level were the only independent predictors of survival outcomes.\textsuperscript{60} However, in this trial, patients were monitored by disease-specific primers for molecular relapse (MRD), and those who relapsed received rituximab as re-induction but were not considered to have relapsed unless there was morphologic evidence of relapse.

The Cancer and Leukemia Group B (CALGB 59909 trial) reported that rituximab in combination with methotrexate and augmented CHOP followed by HDT/ASCR was safe and effective in patients with newly diagnosed MCL (n=78).\textsuperscript{56} At a median follow-up of 4.7 years, the 5-year PFS and OS rates were 56\% and 64\%, respectively.\textsuperscript{56}

In newly diagnosed patients with MCL (n=88 evaluable), sequential chemotherapy (CHOP followed by ICE) with or without rituximab followed by consolidation with HDT/ASCR was associated with a superior PFS compared with RIT followed by CHOP (4-year PFS rate: 65\% vs. 26\%); the 4-year OS rate was 84\% for both treatment groups.\textsuperscript{16} This study also demonstrated the prognostic significance of the proliferation index on PFS outcomes. Moreover, among the subgroup of
patients with a proliferation index <30%, HDT/ASCR resulted in superior PFS compared with RIT-CHOP (5-year PFS rate: 82% vs. 24%). In the phase III randomized Intergroup trial conducted by the European MCL Network, sequential treatment with 3 cycles each of R-CHOP and R-DHAP followed by HDT/ASCR (using high-dose cytarabine containing myeloablative regimen) induced higher remission rates compared with 6 cycles of R-CHOP followed by HDT/ASCR (using myeloablative radiochemotherapy) in patients (age ≤ 65 years) with advanced stage MCL (391 evaluable patients). The clinical CR rate was 39% and 26%, respectively; median time to treatment failure (TTF) was not reached in the R-CHOP/R-DHAP arm compared with 49 months in the R-CHOP arm, after a median follow up of 27 months. The rate of molecular remission (MRD-negative status in peripheral blood or bone marrow) was significantly higher in the R-CHOP/R-DHAP arm compared with R-CHOP (73% vs. 32%). Achievement of molecular remission in the bone marrow after induction was associated with significantly improved 2-year PFS outcomes in the combined treatment arms. Final analysis from this trial (455 evaluable patients) confirmed that R-CHOP/R-DHAP induction was associated with higher CR rate (36% vs. 25%) and CR/CRu rate (54% vs. 40%) compared with R-CHOP. After HDT/ASCR, the CR rates were similar between treatment arms (61% vs. 63%), although R-CHOP/R-DHAP was associated with longer remission duration (84 months vs. 49 months; \( P = .0001 \)). After a median follow up of 51 months, median TTF was significantly longer in the R-CHOP/R-DHAP arm compared with the R-CHOP arm (88 months vs. 46 months; \( P = .038 \)). Moreover, median OS was longer in the R-CHOP/R-DHAP arm (not reached vs. 82 months; \( P = .045 \)). The investigators concluded that an induction regimen containing high-dose cytarabine in addition to R-CHOP resulted in improved outcomes, and suggested that these regimens followed by HDT/ASCR may define a new standard for the treatment of younger patients (<65 years of age) with MCL.

In a phase II multicenter trial of the French cooperative group GELA, induction with 3 cycles each of R-CHOP and R-DHAP resulted in an ORR of 95% with CR in 57% of patients (age ≤ 65 years) with previously untreated MCL (n=60). Patients went on to receive HDT/ASCR on this study. After a median follow up of 67 months, the median EFS was 83 months and median OS has not been reached; the 5-year OS was 75%.

**Post-induction Maintenance Therapy**

Maintenance therapy with rituximab may provide extended disease control for patients who are not physically fit or not eligible to undergo aggressive first-line treatment regimens and HDT/ASCR.

In a small phase II pilot study in previously untreated patients (n=22), a less intensive, modified R-hyper-CVAD regimen (without methotrexate or cytarabine, and with modifications to dose schedule of vincristine and steroids) followed by rituximab maintenance for 5 years resulted in a median PFS of 37 months with median OS not reached; the use of rituximab maintenance appeared to prolong PFS with acceptable toxicity.

In a subsequent study that incorporated the proteasome inhibitor bortezomib into the modified R-hyper-CVAD (VcR-CVAD regimen) followed by rituximab maintenance in patients with previously untreated MCL (n=30), the CR/CRu rate was 77%. After a median follow up of 42 months, median PFS and OS had not been reached. The 3-year PFS rate was 63% and OS rate was 86%. This VcR-CVAD regimen with maintenance rituximab was further evaluated in a larger phase II ECOG trial (E1405) in patients with previously untreated MCL (n=75).
The ORR in this trial was 95% with CR in 68% of patients. Following induction therapy, patients proceeded with maintenance rituximab (n=44) or consolidation with stem cell transplantation (SCT) off protocol (n=22). After a median follow up of 4.5 years, the 3-year PFS and OS rates were 72% and 88% respectively. No differences in PFS or OS were observed between patients who went on to receive rituximab maintenance or SCT.64

The European MCL Network recently conducted a phase III randomized trial in older patients (age >60 years not eligible for HDT/ASCR) with previously untreated MCL (n=560; 485 patients evaluable for response) to evaluate induction with R-FC (rituximab, fludarabine and cyclophosphamide) versus R-CHOP, with a second randomization to maintenance with rituximab every 2 months (until relapse; thus, there was no set duration of maintenance rituximab) versus interferon-alpha (given until progression in both arms).63 Response after induction therapy with R-CHOP and R-FC was similar (CR rate: 34% vs. 40%; CR/CRu rate: 49% vs.53%; ORR: 86% vs. 78%, respectively), but more patients progressed during R-FC than with R-CHOP (14% vs. 5%). Median duration of response was similar between R-FC and R-CHOP arms (37 months vs. 36 months). OS (from start of induction) was significantly longer with R-CHOP compared with R-FC (Median OS: 67 months vs. 40 months; 4-year OS: 62% vs. 47%; P=0.005).63 Grade 3-4 hematologic toxicities occurred more frequently with R-FC induction.

Among the patients who responded to induction and underwent second randomization (n=316), median remission duration was significantly improved with rituximab maintenance compared with interferon alfa (75 months vs. 27 months; P <.001). After a median follow up of 42 months, OS outcomes were not significantly different between the two maintenance arms (4-year OS: 79% with rituximab vs. 67% with interferon alfa).63 However, in the subgroup of patients treated with R-CHOP induction (n=184), median OS (from end of induction) was significantly longer with rituximab maintenance compared with interferon alfa (not reached vs. 64 months; 4-year OS: 87% vs. 63%; P=0.005). Moreover, grade 3-4 hematologic toxicities occurred more frequently with interferon alfa. Rituximab was associated with more frequent grade 1-2 infections.63 This study suggests that for patients who are not candidates for HDT/ASCR as part of first-line therapy, R-CHOP induction followed by rituximab maintenance may offer the best chance to prolong remission duration. Given the positive outcomes reported in this study (with median duration of response exceeding 6 years with rituximab maintenance and a 4-year OS rate of 87% in patients treated with R-CHOP and rituximab maintenance), it is unknown whether first-line consolidation with HDT/ASCR provides an advantage over rituximab maintenance in patients of any age. At the present time, no data are available from randomized studies that would allow direct comparison of outcomes with these two different consolidation approaches.

**Relapsed or Refractory Disease**

**Second-line Therapy**

The treatment of patients with relapsed/refractory MCL remains a major challenge, as CR rates are generally low (<30%) and response durations are limited with available regimens.65

Bortezomib is a proteasome inhibitor with activity in patients with relapsed or refractory MCL,42-44 and is currently approved for the treatment of patients with MCL that has relapsed after at least one prior therapy. FDA approval of this agent was based on data from the pivotal phase II PINNACLE trial of single-agent bortezomib in patients with relapsed/refractory MCL (n=155; 141 evaluable patients).42 In this trial, bortezomib induced an ORR of 33% (CR in 8%), with a median duration of response of 9 months.42 Median time to progression (in all patients)
was 6 months. Longer follow-up data also confirmed these initial findings; after a median follow-up time of 26 months, the median OS in all patients was 23.5 months and was 35 months in responding patients. Small studies have reported promising activity of bortezomib combined with rituximab in heavily pretreated patients with relapsed/refractory MCL. In addition, bortezomib in combination with R-hyper-CVAD, with (as discussed above) or without rituximab maintenance, is under investigation in previously untreated patients with MCL.

Cladribine has shown activity as a single agent in patients with relapsed MCL. In the trial conducted by the North Central Cancer Treatment group, the ORR and median PFS for patients with recurrent MCL (n=25) were 46% (21% CR) and 5 months, respectively. Fludarabine-based combination regimens, with or without rituximab, have also shown activity in patients with relapsed or refractory MCL. Results from a small pilot trial in patients with newly diagnosed and relapsed MCL (20 evaluable patients) showed that the combination of fludarabine, mitoxantrone and rituximab (FMR) induced a CR rate of 90%, with a median duration of CR of 17 months. In patients with MCL (n=66) treated as part of a prospective randomized phase III study of the GLSG, the addition of rituximab to the combination of fludarabine, cyclophosphamide and mitoxantrone (FCM) [R-FCM regimen], produced higher ORR (58% vs. 46%) and CR rates (29% vs. 0%) compared with FCM alone. This trial included a second randomization to rituximab maintenance versus observation in patients who responded to therapy. In the subgroup of patients with MCL who received R-FCM induction (n=47), rituximab maintenance resulted in a higher proportion of patients in remission beyond 2 years compared with observation only (45% vs. 9%; P=0.049); the median duration of remission was similar between maintenance and observation arms (14 months vs. 12 months).

Fludarabine combined with rituximab (FR) was evaluated as part of a phase III randomized trial from StiL that compared FR versus BR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%). Following a protocol amendment, maintenance therapy with rituximab was also added in both treatment arms (n=40 only). The FR regimen resulted in an ORR and CR rate of 52.5% and 16%, respectively, which was significantly inferior to response rates with BR (ORR 83.5%; CR rate 38.5%). The median PFS with FR was 11 months, which was also significantly shorter compared with a median of 30 months observed with the BR regimen (P <.0001). However, no difference in median OS was observed between treatment arms after a median observation time of 33 months.

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in patients with heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies as well as aggressive lymphomas. In a phase II multicenter study, BR resulted in an ORR of 92% (41% CR) in patients with relapsed or refractory indolent lymphomas and MCL (n=67). The median duration of response and PFS was 21 months and 23 months, respectively. Outcomes were similar for patients with indolent or mantle cell histologies. For the subgroup of patients with MCL histology (n=12), the ORR was 92% (42% CR; 17% CRu) and the median duration of response was 19 months. As discussed above, the phase III randomized trial from StiL showed superiority of the BR regimen compared with FR in patients with relapsed/refractory follicular or indolent lymphoma or MCL (208 evaluable patients; MCL histology in about 20%), with an ORR of 83.5% (38.5% CR) and median PFS of 30
In a small multicenter phase II study that evaluated the combination of bendamustine and rituximab with bortezomib in patients with relapsed/refractory indolent lymphomas or MCL (29 evaluable patients; MCL histology, n=7), the ORR was 83% (52% CR) and the 2-year PFS rate was 47%. The ORR among the small subgroup of patients with MCL was 71%. Based on these results, this combination regimen is currently being evaluated in randomized trials conducted by the US cooperative groups.

Lenalidomide is an immunomodulating agent that has been evaluated as a single agent in patients with relapsed or refractory aggressive NHL in two phase II studies (NHL-002 and NHL-003). In the subset analysis of patients with MCL (n=15) in the NHL-002 study, the ORR was 53% (20% CR). The median duration of response and PFS were 14 months and 6 months, respectively. The subset analysis of patients with MCL (n=54) enrolled in the larger confirmatory study (NHL-003) also showed similar results with an ORR of 43% (17% CR). An updated analysis from the NHL-003 study showed that in the relapsed/refractory MCL subgroup (n=57), the ORR with single-agent lenalidomide was 35% (12% CR/CRu) by independent central review at a median follow up of 12 months. The ORR by investigator review was 44% (21% CR/CRu). By central review, the median duration of response was 16 months and the median PFS was approximately 9 months. Additional phase II studies are specifically evaluating the role of single-agent lenalidomide in patients with relapsed/refractory MCL. In a phase II study in patients with relapsed/refractory MCL (n=26), lenalidomide (including low-dose lenalidomide maintenance in responding patients) resulted in an ORR of 31% with a median response duration of 22 months. The median PFS was only 4 months. However, among the patients who received maintenance lenalidomide (n=11), the median PFS was 15 months. In a larger multicenter phase II study (MCL-001) in patients who relapsed after or were refractory to bortezomib (n=134; median 4 prior therapies), lenalidomide as single agent resulted in an ORR of 28% (7.5% CR/CRu) by independent central review. All patients were previously treated with rituximab-containing regimens, and all had relapsed or were refractory to bortezomib. The median duration of response was 16.6 months. The median PFS and OS were 4 months and 19 months respectively. In the larger studies, the most common grade 3 or 4 toxicities with lenalidomide were myelosuppression (neutropenia in 43%-46% and thrombocytopenia in 28%-30%). Lenalidomide combined with rituximab is also under clinical evaluation. In a phase I/II study of a combination regimen with lenalidomide and rituximab in patients with relapsed/refractory MCL (36 evaluable patients), the ORR was 53% (31% CR). The median duration of response was 18 months, and the median PFS (for all patients in the phase II portion) was 14 months. In an updated analysis of this study (n=52), the ORR was 57% (36% CR) among patients treated in the phase II portion (n=44); median duration of response was 19 months. The median PFS was 11 months and median OS was 24 months. The most common grade 3 or 4 toxicities included neutropenia (66%) and thrombocytopenia (23%).

Ibrutinib is a small-molecule inhibitor of Bruton’s tyrosine kinase (BTK) involved in the B-cell signalling pathway and has shown promising activity in patients with B-cell malignancies. In a phase I dose-escalation study in patients with relapsed and/or refractory B-cell malignancies (n=56; follicular lymphoma, 29%; CLL/SLL, 29%; MCL, 16%), ibrutinib given in a continuous or intermittent dosing schedule (until progression) resulted in an ORR of 60% (CR in 16%) among evaluable patients (n=50). The median PFS was approximately 14 months. Among the subgroup of patients with MCL (n=9), response was observed in 7 patients, including a CR in 3 patients. Treatment with
ibrutinib was well tolerated even with prolonged dosing (> 6 months), with no dose-limiting toxicities and no significant myelosuppression; grade 3 or 4 adverse events were uncommon.85 The fixed dose of 560 mg daily given continuously was well tolerated and resulted in full occupancy of the BTK target; thus, the recommended phase II dose was established as 560 mg daily. The results of a multicenter phase II study evaluating ibrutinib (560 mg continuous daily dosing until progression) in patients with relapsed or refractory MCL (n=115; median 3 prior therapies, range 1–5), including in patients previously treated with bortezomib have been published.86 The large majority of patients had received prior rituximab-containing regimens (89%) and 45% were refractory to last therapy before study enrollment. Most patients had advanced disease (72%) and 49% had high-risk disease based on MIPI scores.86 Among 111 evaluable patients, the estimated median follow up was 15 months at the time of analysis. The ORR was 68% with a CR in 21% of patients. The median duration of response was 17.5 months. Among the subgroup of patients who were previously treated with bortezomib (n=48), the ORR was 67% with a CR in 23%. The response rates appeared to increase with longer duration of therapy. The estimated median PFS for all treated patients was approximately 14 months. Median OS has not yet been reached; the estimated OS rate at 18 months was 58%. The most common grade 3 or greater adverse events included neutropenia (16%), thrombocytopenia (11%), anemia (10%), pneumonia (6%), diarrhea (6%), fatigue (5%) and dyspnea (5%).86 This study showed durable responses with single-agent ibrutinib with a favorable toxicity profile. The use of ibrutinib has been known to result in an initial transient lymphocytosis which resolves by a median of 8 weeks after initiation of ibrutinib.87 Ibrutinib treatment has also been associated with grade ≥ 3 bleeding events in 5% of patients.87 The benefit and risk of ibrutinib should be considered in patients requiring anti-platelet or anticoagulant therapies. See “Special Considerations for the use of BCR Inhibitors” in the guidelines for monitoring and management of adverse reactions associated with ibrutinib.

Based on these data, ibrutinib (560 mg orally, once daily) was recently approved by the FDA for the treatment of patients with MCL who received at least one prior therapy.

**Second-Line Consolidation Therapy**

In patients with relapsed/refractory indolent NHL, allogeneic stem cell transplant (SCT) has resulted in decreased rates of disease recurrence compared with HDT/ASCR, but at the cost of a higher treatment-related mortality (TRM) rate.88,89 In an effort to reduce the TRM associated with allogeneic SCT, the use of reduced-intensity conditioning (RIC) regimens has been explored. In a study that evaluated allogeneic SCT using conventional myeloablative conditioning or RIC in patients with relapsed/refractory NHL (n=25), RIC (fludarabine-based regimens) was associated with a decreased TRM rate (17% vs. 54%) and increased event-free survival (50% vs. 23%) and OS (67% vs. 23%) rates at 1 year compared with myeloablative regimens.90 A multicenter retrospective study of RIC allogeneic SCT in patients with relapsed/refractory low-grade NHL (n=73) also reported promising long-term outcomes with RIC (primarily using fludarabine-based regimens); in this study, the 3-year EFS and OS rates were 51% and 56%, respectively.91 Although the 3-year relapse rate appeared low at 10%, the TRM rate was high, with a 3-year cumulative incidence of 40%.91 Allogeneic SCT using RIC has been evaluated as a consolidation strategy for patients in remission following treatment for relapsed/refractory MCL.51,92,93 In patients with relapsed MCL treated with RIC allogeneic SCT (n=18), the 3-year PFS rate and estimated 3-year OS rate was 82% and 85.5%, respectively; the
majority of patients in this study (89%) had chemosensitive disease. In another study, RIC allogeneic SCT was evaluated in patients with relapsed/refractory MCL (n=33); 42% of these patients had failed prior HDT/ASCR. The 2-year disease-free survival and OS rates were 60% and 65%, respectively. The 2-year relapse rate was 9%; moreover, with a median follow up of nearly 25 months, none of the patients transplanted in a CR (n=13) experienced disease relapse. The 2-year TRM rate in this study was 24%. In an analysis of patients with MCL treated with SCT at the MD Anderson Cancer Center, the subgroup of patients with relapsed/refractory disease treated with RIC allogeneic SCT (n=35) had favorable long-term outcomes. Most of these patients (62%) were transplanted in remission (31% in second remission). The analysis reported a median PFS of 60 months, and 6-year PFS and OS rates of 46% and 53%, respectively. The TRM rates at 3 months and 1 year were 0% and 9%, respectively.

**NCCN Recommendations for Stage I-II**

**Recommendations for First-line Therapy and Follow-up**

Outside of a clinical trial, the NCCN Guidelines panel recommends RT (30-36 Gy) alone or combination chemoimmunotherapy with or without RT. These recommendations are based on treatment principles in the absence of more definitive clinical data.

For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically indicated. If the patient received initial treatment with chemoimmunotherapy with or without RT, and relapses after an initial CR (or the initial response is a PR or disease progression on first-line therapy), the patient should be treated with second-line therapy regimens recommended for stage II (bulky) or stage III-IV disease (see sections below). If the patient received initial treatment with RT alone and relapses after achieving a CR (or the initial response is a PR or disease progression with RT alone), then the patient can be treated with first-line induction therapy (comprising chemoimmunotherapy regimens) recommended for stage II (bulky) and stage III-IV disease.

**NCCN Recommendations for Stage II (bulky) and Stage III-IV**

**Recommendations for First-line Therapy and Follow-up**

In the absence of standard management for patients with advanced disease, patients should be referred for participation in prospective clinical trials. Similar to the management of patients with indolent lymphomas, patients with MCL often require highly individualized courses of care. The majority of patients with MCL will have advanced stage disease and require systemic therapy. However, in highly selected patients with asymptomatic disease, close observation with deferred therapy is a reasonable option, especially for those with good performance status and lower risk scores on standard IPI.

The standard treatment regimen for MCL is not yet established. There are no prospective randomized studies comparing the various aggressive induction regimens for MCL, although some randomized data exist for less intensive first-line treatment options (as previously discussed). Given the role of rituximab in the treatment of CD20-positive NHL, it is reasonable to consider rituximab-containing regimens for management of advanced MCL. Based on the available data, the NCCN Guideline panel has included the following regimens for initial induction therapy:

**Aggressive Therapy**

All regimens listed below (except for hyper-CVAD + rituximab) included first-line consolidation with HDT/ASCR in published reports.

- Hyper-CVAD + rituximab\(^ {32-34}\)
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Non-Hodgkin’s Lymphomas

- Dose-intensified CHOP [maxi-CHOP] alternating with rituximab + high-dose cytarabine (NORDIC regimen)\textsuperscript{55}
- Rituximab and methotrexate with augmented CHOP (CALGB regimen)\textsuperscript{16}
- Sequential R-CHOP and R-ICE\textsuperscript{16}
- Alternating R-CHOP and R-DHAP\textsuperscript{57}

Less aggressive therapy:
- Bendamustine + rituximab\textsuperscript{57}
- Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP)\textsuperscript{45}
- Cladribine + rituximab\textsuperscript{39,41}
- CHOP + rituximab (R-CHOP)\textsuperscript{29,36}
- Modified Hyper-CVAD with rituximab maintenance in patients older than 65 years\textsuperscript{61}

For patients with a CR to first-line therapy, participation in a clinical trial or HDT/ASCR is recommended for eligible patients (see section below). For patients with a CR, clinical follow up should be conducted every 3-6 months for the first 5 years, and then on a yearly basis or as clinically indicated. For patients with only a PR to first-line therapy, additional therapy (see second-line therapy regimens below) may be considered in an effort to improve the quality of a response. If the patient achieves a CR (or improved PR) with additional therapy, consolidation with HDT/ASCR may be considered for eligible patients, as discussed above. For patients who relapse after achieving a remission to first-line therapy, or for patients who experience disease progression during initial therapy, participation in clinical trials is preferred. In the absence of suitable clinical trials, second-line treatment options can be considered.

Recommendations for First-line Consolidation Therapy
The panel recommends consolidation with HDT/ASCR for eligible patients in remission following first-line therapy, although no studies have compared maintenance rituximab with HDT/ASCR for patients in first CR. In general, patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive induction therapy followed by consolidation with HDT/ASCR or maintenance rituximab may also result in good long-term outcome.

For patients who are not candidates for HDT/ASCR, and who are in remission after first-line therapy with R-CHOP, maintenance treatment with rituximab (every 8 weeks until disease progression) is recommended (category 1)\textsuperscript{63}

Recommendations for Second-line Therapy
The optimal approach to relapsed or refractory disease remains to be defined. Patients with relapsed disease following CR to induction therapy or those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials involving HDT/ASCR or allogeneic HSCT, immunotherapy with nonmyeloablative stem cell rescue or treatment with new agents. Based on the recent FDA approval, the panel has included ibrutinib as an option for second-line therapy for patients with relapsed or refractory disease.\textsuperscript{86} Alternatively, in the absence of an appropriate clinical trial, these patients can be treated with second-line chemotherapy regimens (with or without rituximab) recommended for patients with DLBCL or any of the following regimens:

- Bendamustine ± rituximab\textsuperscript{74}
- Bortezomib ± rituximab\textsuperscript{66,67}
- Cladribine ± rituximab\textsuperscript{39,40}
FC (fludarabine, cyclophosphamide) ± rituximab

FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

FMR (fludarabine, mitoxantrone, rituximab)

Lenalidomide ± rituximab

PCR (pentostatin, cyclophosphamide, rituximab)

PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab

Allogeneic transplantation (with myeloablative or reduced intensity conditioning) is an appropriate option for patients with relapsed or refractory disease that is in remission following second-line therapy.
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