# AHFS Final Determination of Medical Acceptance:
# Off-label Use of Rituximab in Combination with Bendamustine for the Treatment of Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma

**Drug/Drug Combination:** Rituximab in combination with bendamustine

**Off-label Use:** Relapsed or refractory indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma

**Criteria Used in Selection of Off-label Use for Review:**

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in October 2008. In 2008, indolent non-Hodgkin's lymphoma and mantle cell lymphoma were addressed separately; however, the current review combined both indications into one determination. At the time of the original review, the use of rituximab in combination with bendamustine for relapsed or refractory indolent non-Hodgkin's lymphoma was a reasonable choice (accepted, with possible conditions) in patients with relapsed or refractory, non-transformed, low-grade non-Hodgkin's lymphoma; the use of rituximab in combination with bendamustine for relapsed or refractory mantle cell lymphoma was a reasonable choice (accepted, with possible conditions) in patients with relapsed disease.

**Strength of Evidence:** Level 3 (Low strength/quality)

**Strength of Study End Point(s):** Progression-free survival

**Grade of Recommendation:** Recommended use (Accepted)

**Narrative Summary:**

*Relapsed or Refractory Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma:*

Efficacy and safety of bendamustine in combination with rituximab† for the treatment of relapsed or refractory† indolent NHL or relapsed or refractory mantle cell lymphoma† in patients who had received up to 3 prior treatment regimens has been studied in 2 open-label, phase 2 studies.[10002, 10003]

In the first study, 63 patients received rituximab 375 mg/m$^2$ as an IV infusion on day 1, followed by bendamustine hydrochloride 90 mg/m$^2$ daily as an IV infusion on days 2 and 3, administered on a 28-day cycle for a total of 4 cycles.[10002] An additional dose of rituximab was administered one week prior to the first bendamustine-rituximab treatment cycle and repeated at 28 days following the last bendamustine-rituximab treatment cycle.[10002] Patients with relapsed or refractory mantle cell lymphoma or indolent NHL, including the histologic subtypes follicular lymphoma (grade 1 or 2), Waldenstrom macroglobulinemia, and marginal-zone lymphoma, were eligible for enrollment in the study.[10002] Patients who previously received immunotherapy (i.e., rituximab) were excluded from the study.[10002] The median patient age was 64 years; 38% of patients had follicular lymphoma, 27% had Waldenstrom macroglobulinemia, and 25% had mantle cell lymphoma.[10002] Most patients (68%) enrolled in the study had received 1 prior therapy for their disease and 30% of patients

were refractory to their last prior therapy.[10002] The primary efficacy end point was progression-free survival.[10002] At a median follow-up of 20 months, median progression-free survival was 24 months.[10002] Overall response rate was 90%; 60% of patients achieved complete response.[10002] Median progression-free survival for the 16 patients with mantle cell lymphoma was 18 months and overall response rate was 75%; 50% of patients with mantle cell lymphoma achieved complete response.[10002] Median overall survival had not been reached at the time of analysis; however, the actuarial 48-month survival rate was 55%.[10002] Grade 3 or 4 leukopenia, thrombocytopenia, and anemia occurred during 16, 3, and 1% of treatment cycles, respectively.[10002]

In the second study, 66 patients received rituximab 375 mg/m$^2$ on day 1, followed by bendamustine hydrochloride 90 mg/m$^2$ daily as an IV infusion on days 2 and 3, administered on a 28-day cycle for a total of 4 cycles.[10003] An additional dose of rituximab was administered one week prior to the first bendamustine-rituximab treatment cycle and repeated at 28 days following the last bendamustine-rituximab treatment cycle.[10003] Patients achieving a response between the second and fourth treatment cycles were permitted to receive an additional 2 cycles of bendamustine-rituximab treatment.[10003] Patients with relapsed, CD20-positive mantle cell lymphoma or indolent NHL, including the histologic subtypes follicular lymphoma, small lymphocytic lymphoma, Waldenstrom macroglobulinemia, and marginal-zone lymphoma, were eligible for enrollment in the study.[10003] Patients who received prior radioimmunotherapy or high-dose chemotherapy with allogeneic stem-cell transplantation, those receiving concurrent therapy with therapeutic dosages of systemic corticosteroids, and those with rituximab-refractory disease were excluded from the study.[10003] The median patient age was 60 years; 61% of patients had follicular lymphoma, and 18% had mantle cell lymphoma.[10003] All patients enrolled in the study had a World Health Organization (WHO) performance status of 0–2.[10003] The primary efficacy end point was overall response rate.[10003] At a median follow-up of 20 months, the overall response rate was 92%; 41% of patients achieved complete response.[10003] The median duration of response for all responders was 21 months (range: 18–24 months).[10003] Among patients who received prior therapy with rituximab or those who were rituximab-naive, the overall response rate was 86 or 100%, respectively, and the complete response rate was 35 or 48%, respectively.[10003] At the time of analysis, median progression-free survival was 23 months.[10003] Overall response rate for the 12 patients with mantle cell lymphoma was 92% with a median duration of response of 19 months; 42% of patients with mantle cell lymphoma achieved complete response.[10003] Grade 3 or 4 leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, and anemia occurred in 30, 36, 6, 9, and 2% of patients, respectively.[10003]

Based on current evidence and because of the favorable toxicity profile,[10002, 10003] combination therapy with bendamustine and rituximab is recommended (accepted) for use in the treatment of relapsed or refractory indolent NHL or mantle cell lymphoma.

*Dosage*:

When bendamustine has been used in combination with rituximab† in adults with relapsed or refractory† indolent NHL or relapsed or refractory mantle cell lymphoma†, rituximab 375 mg/m$^2$ has been administered by IV infusion on day 1, followed by IV infusion (over 30–60 minutes) of bendamustine hydrochloride 90 mg/m$^2$ on days 2 and 3.[10002, 10003] The bendamustine-rituximab regimen has been administered on a 28-day cycle for a total of 4–6 cycles.[10002, 10003] An additional dose of rituximab has been administered one week prior to the first bendamustine-rituximab treatment cycle and repeated at 28 days following the last bendamustine-rituximab treatment cycle.[10002, 10003]

**References:**

10002. Rummel MJ, Al-Batran SE, Kim SZ et al. Bendamustine plus rituximab is effective and has a favorable toxicity in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin*

*Oncol.* 2005; 23:3383-9.

10003. Robinson KS, Williams ME, van der Jagt RH et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2008; 26:4473-9.

**Oncology Expert Committee Voting Results:**

*Proposed Level of Evidence:* Level 3 (Low strength/quality); progression-free survival

Concur with rating: 4 votes

Do not concur with rating: 1 vote (Level 2)

*Grade of Recommendation:*

Recommended use (Accepted): 3 votes

Reasonable choice (Accepted, treatment option): 2 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

*Proposed Consensus Recommendation:*

Based on current evidence and because of the favorable toxicity profile, combination therapy with bendamustine and rituximab is recommended (accepted) for use in the treatment of relapsed or refractory indolent NHL or mantle cell lymphoma.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

**Oncology Expert Committee Members' Comments:**

*Comments in Support of Vote on Level of Evidence and Grade of Recommendation*:

Reviewer #1: [Efficacy] based on overall response rate in indolent lymphoma and mantle cell lymphoma.

Reviewer #3: This [Rituximab in combination with bendamustine] is a reasonable option for these patients with relapsed indolent mantle cell lymphoma or indolent non-Hodgkin's lymphoma. Thank you for the opportunity to review and respond.

Reviewer #4: [Specific patient population] Less toxicity, better progression-free survival, and equal overall survival [in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma].

Reviewer #5: [Specific patient population] Not indicated for rituximab refractory disease as these were excluded from references 10003 and 10002 [in patients with indolent NHL].

[Specific patient population] Not indicated for rituximab refractory disease [in patients with mantle cell lymphoma].

*Comments on Draft Narrative Summary:*

Reviewer #5: Prior [use of] rituximab excluded from both studies.

*Comments on Proposed Consensus Recommendation*:
None.

**Participants:**

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Beth Faiman, Ph.D., RN, ANP-BC, AOCN; Raymond Hohl, M.D., Ph.D.; LeAnne Kennedy, Pharm.D., BCOP; Sandra Kurtin, RN, MS, AOCN, ANP-C; LeAnn Norris, Pharm.D., BCPS, BCOP

External Consultants: None

**Conflict of Interest Disclosures:**

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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