

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
First-line therapy for advanced-stage, indolent non-Hodgkin's lymphoma	Bendamustine-Rituximab (BR) regimen Rituximab 375 mg/m ² on day 1; Bendamustine 90 mg/m ² IV on days 1 and 2. Cycle repeats every 28 days for a total of 6 cycles. ¹	Low quality; Progression-free and relapse-free survival ¹	Not fully established	One reviewer self-recused, citing a direct conflict with Cephalon; the individual's comments were not shared with the remaining committee members, and the individual did not participate in the consensus vote.	October 2008
First-line therapy for advanced-stage mantle cell lymphoma	Bendamustine-Rituximab (BR) regimen Rituximab 375 mg/m ² on day 1; Bendamustine 90 mg/m ² IV on days 1 and 2 Cycle repeats every 28 days for a total of 6 cycles. ¹	Low quality Progression-free and relapse-free survival ¹	Not fully established	One reviewer self-recused, citing a direct conflict with Cephalon; the individual's comments were not shared with the remaining committee members, and the individual did not participate in the consensus vote.	October 2008
Relapsed refractory, indolent non-Hodgkin's lymphoma	Bendamustine-Rituximab (BR) regimen Rituximab 375 mg/m ² IV infusion on day 1 followed by bendamustine 90 mg/m ² as an IV infusion over 30–60 minutes on days 1 and 2. ^{2,3} An additional dose of rituximab was given 7 days prior to the first cycle and then repeated 28 days after the completion of the last cycle. ^{2,3} Cycle repeats every 28 days for a total of 4 cycles. ^{2,3} In the second study, an additional 2 cycles were permitted for patients achieving a response between cycles 2 and 4. ³	Low quality; Progression-free survival ^{2,3}	Reasonable choice in relapsed/refractory, non-transformed, low-grade NHL (Accepted)	One reviewer self-recused, citing a direct conflict with Cephalon; the individual's comments were not shared with the remaining committee members, and the individual did not participate in the consensus vote.	October 2008

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
Relapsed, refractory mantle cell lymphoma	<p>Bendamustine-Rituximab (BR) regimen</p> <p>Rituximab 375 mg/m² IV infusion on day 1, followed by bendamustine 90 mg/m² as an IV infusion over 30–60 minutes on days 1 and 2.^{2,3} An additional dose of rituximab was given 7 days prior to the first cycle and then repeated 28 days after the completion of the last cycle.^{2,3}</p> <p>Cycle repeats every 28 days for a total of 4 cycles.^{2,3} In the second study, an additional 2 cycles were permitted for patients achieving a response between cycles 2 and 4.³</p>	<p>Low quality; Progression-free survival²</p> <p>Duration of response³</p>	Reasonable choice in relapsed mantle cell lymphoma (Accepted)	One reviewer self-recused, citing a direct conflict with Cephalon; the individual's comments were not shared with the remaining committee members, and the individual did not participate in the consensus vote.	October 2008
Relapsed rituximab- refractory, indolent, non-Hodgkin's lymphoma ^a	<p>Bendamustine monotherapy regimen</p> <p>Bendamustine 120 mg/m² as an IV infusion on days 1 and 2.</p> <p>Cycle repeats every 21 days for a total of 6 cycles (2 additional cycles may be administered if clinical benefit observed)^{4,5}</p>	Low quality; Progression-free survival ^{4,5}	Reasonable choice in rituximab- refractory, low- grade, NHL (Accepted)	One reviewer self-recused, citing a direct conflict with Cephalon; the individual's comments were not shared with the remaining committee members, and the individual did not participate in the consensus vote.	October 2008

^a Bendamustine was FDA approved for relapsed non-Hodgkin's lymphoma, who have progressed following a rituximab-containing regimen, on October 31, 2008.

Bendamustine-Rituximab as first-line therapy for adult indolent non-Hodgkin's lymphoma and mantle cell lymphoma (StiL Study)

- The combination of bendamustine and rituximab (BR) has been compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in a phase III randomized study to safety and efficacy of the BR regimen in patients with newly diagnosed indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma.¹
- Patients (n=463) were randomized to receive either R-CHOP or BR for a total of 6 cycles.¹ The primary end point was event-free survival (EFS).¹
- The median age for both treatment arms was 64 years; a similar percentage of patients was older than 60 years of age in both groups (61 and 64% for BR and R-CHOP, respectively).¹
- In both treatment arms, similar percentages reflected the indolent histologies: follicular (51 and 55% of patients receiving BR and R-CHOP, respectively), immunocytoma/small lymphocytic leukemia (SLL) (14% of each group of patients receiving BR and R-CHOP), and marginal zone (15 and 12% of patients receiving BR and R-CHOP, respectively).¹
- Patients with mantle cell lymphoma represented 20 and 18% of the study population in the BR and R-CHOP arms, respectively.¹
- Based on the first interim results for 315 patients (i.e., 68% of those enrolled) and a median observation period of 18 months, the overall response rate (ORR) for both groups was identical (93%).¹ The complete response (CR) rates were 47 and 42%, and stable disease (SD) rates were 3 and 4% for BR and R-CHOP, respectively.¹ The progressive disease/relapse rates were higher with R-CHOP compared with BR (43 versus 33%, respectively); however, the number of deaths was similar for both treatment arms (13 and 12 for BR and R-CHOP, respectively).¹
- In patients with follicular lymphoma (which represented the largest subset of the study population by histology), ORR was 96 and 93% for BR and R-CHOP, respectively; however, the CR rate was higher with the BR regimen (51 and 43% with BR and R-CHOP, respectively).¹ The ORR and CR rates were higher for BR for the immunocytoma/SLL cohort compared with R-CHOP; higher ORR and CR rates were reported with R-CHOP for the marginal zone subset.¹
- In the mantle cell cohort, the ORR was higher with R-CHOP than with BR (96 versus 88%, respectively), yet the CR rates were similar for both groups (41 and 42% for R-CHOP and BR, respectively).¹
- Alopecia was reported in 94% of the patients receiving R-CHOP compared with 0% in the BR group.¹ Both grade 3/4 leukopenia and infectious complications were higher with R-CHOP than with BR (grade 3/4 leukopenia: 41 versus 16%, respectively; infectious complications: 41 and 23%, respectively).¹
- A nonsignificant improvement in PFS and relapse-free survival has been reported with BR.¹ Based on data for responding patients (i.e., those achieving at least a partial response), the relapse-free survival was similar for patients achieving either a CR or a PR; however, no direct comparison between the 2 treatment arms has been made.¹ To date, the survival data have been reflected as an aggregate; specific information has not been reported for the mantle cell lymphoma subset.¹

Bendamustine-Rituximab (BR) for relapsed/refractory indolent adult non-Hodgkin's lymphoma.

- Two open label, phase II studies have been conducted with the BR regimen in patients with relapsed/refractory indolent NHL.^{2,3} The median patient age in the first study was 64 years old;² in the second study, the median age was 60 years.³
- The first study excluded patients who had received a prior rituximab-containing regimen; therefore, only patients who had received either single-agent or combination chemotherapy regimens were eligible to receive BR.² Sixty-eight percent of the patients had received one prior regimen, 19% had received 2 regimens, and 13% had received 3 prior regimens.² Thirty percent of the patients in this study were refractory to their last regimen.²
- In the second study, patients were allowed to have had up to 3 prior regimens, including a rituximab-containing regimen, as long as their disease was not characterized as refractory.³ The mean number of prior regimens was 1.6; alkylator-based therapy had been used in 85%, purine analog-based therapy in 23%, and anthracycline-based therapy in 58%.³ Rituximab had been given to 56% of the patients with a mean of 1.3 distinct regimens.³

- No patients in either study had received prior radioimmunotherapy.^{2,3}
- The regimen used in both studies employed the BR schedule plus 2 additional doses of rituximab (one dose administered 7 days prior to and a second dose given 28 days after the last cycle of BR).^{2,3} In the second study, 2 additional cycles could be administered if response was evident between the second and fourth cycles.³
- ORR rates of 90 and 92% were reported for all patients in the first and second study, respectively, with CR rates of 60 and 41%, respectively.^{2,3} In the second study, the ORR and CR rate for patients with an indolent histology was 93 and 41%, respectively.³ Patients in this study who had no prior exposure to rituximab had higher ORR and CR + unconfirmed complete response (Cru) rates (100 and 62%, respectively) compared with those with prior rituximab exposure (87 and 49%, respectively).³
- The median PFS for all patients was similar in the first and second studies (24 and 23 months, respectively).^{2,3} The median PFS reported in the first study was considerably prolonged at 24 months compared with a median PFS of 9 months reported with the patient's most recent therapy (p=0.0001).² Patients in the second study who had prior exposure to rituximab had a median duration of response of 21 months, which was the same as the duration of response for the overall study group.³ The duration was slightly shorter (19 months) in patients who had received 2 or more prior chemotherapy regimens.³
- The median survival has not been reached for the patients in the first study; however, an actuarial survival rate of 55% has been reported at 48 months.² Long-term survival data has not been reported in the second study.³
- Data from the subset analysis of mantle cell lymphoma patients, based on a sample sizes of 16 and 12 patients in the first and second studies, respectively, showed ORR and CR rates of 75 and 50%, respectively, in the first study and 92 and 42%, respectively, in the second study.^{2,3} A median PFS of 18 months has been reported in the first study.² The median duration of response has been reported as 19 months in the second study.³
- Grade 3/4 leukopenia was reported in 16 and 30% of patients in the first and second studies.^{2,3} A 37% incidence of neutropenia with a 7% incidence of febrile/neutropenic events was reported in the first study;² a 10% (i.e., grade 3/4) infection rate was reported in both studies.^{2,3} Grade 3/4 thrombocytopenia was reported in 3 and 10% of patients in the first and second studies, respectively.^{2,3}

Bendamustine as monotherapy for relapsed rituximab-refractory non-Hodgkin's lymphoma.

- Two studies (one phase III and one phase II) have reported results with bendamustine as monotherapy of indolent NHL in patients with documented refractoriness to rituximab, defined as the lack of a response or progression within 6 months of completing therapy;^{4,5} in the phase II study, patients could be intolerant of continued treatment with rituximab.⁵ The median age was 60 and 63 years for the phase III and phase II studies, respectively.^{4,5}
- The mean number of prior treatments was 2 in each study;^{4,5} 31.5–36% of the study patients were considered refractory to their last therapy.^{4,5}
- Patients with transformed disease, representing 20% of the study population, were also enrolled in the phase II study.⁵
- In the phase III, single arm, open-label study, patients (n=100) received bendamustine as monotherapy for a total of 6 cycles.⁴ A similar regimen was used in the phase II study (n=76) but the patients were allowed to continue additional therapy until either disease progression occurred or toxicity developed.⁵
- The ORR and CR + CRu rates for patients in the phase III study were 75 and 17%, respectively.⁴ Compared with patients with refractory disease, patients who were considered sensitive to their most recent therapy had considerably higher rates for ORR (88 versus 64% for the sensitive and refractory patients, respectively) and CR + CRu (30 and 6% for the sensitive and refractory patients, respectively).⁴
- Based on a follow-up of 11.8 months in the phase III study, the mean duration of response was 9.2 months for all patients, 10 months for patients with sensitive disease, and 6.3 months for patients with refractory disease.⁴
- In this study, the median PFS was reported as 9.3 months for all patients; PFS was 11.8 months for sensitive-disease patients but was shorter (7.5 months) for refractory disease patients.⁴

- Dosage modifications were required for 18% of the total cycles administered, including 6.7% for neutropenia and 4.9% for thrombocytopenia.⁴ Grade 3/4 lymphopenia was reported in 94% of patients, neutropenia in 61%, and febrile/neutropenia in 6%.⁴
- Within the phase II study, the ORR and CR + CRu rates were 77 and 34%, respectively.⁵ High (67%) ORR rates were reported for the patients with transformed disease; however, the CR + CRu rate was lower at 13%.⁵
- Based on a follow up of 26 months, the mean duration of response was 6.7 months for all patients, 9 months for indolent (or nontransformed) patients, and only 2.3 months for patients with evidence of transformation.⁵ Thirty-six percent of these responses lasted beyond 1 year.⁵
- The median PFS for all patients was reported as 7.1 months; 8.3 and 4.2 months for the indolent and transformed subgroups, respectively.⁵
- The median duration of response was prolonged in patients who had only received 1 or fewer prior regimens compared with those who had received 2 or more prior regimens (9 and 5.3 months, respectively).⁵
- An ORR of 61% was reported in patients with alkylator-refractory disease; a slightly longer response duration was seen in patients with alkylator-refractory compared with those with sensitive disease (7.7 and 6.5 months, respectively).⁵ High overall response rates were also reported in patients who were fludarabine-refractory and also in patients treated with 2 or more prior regimens.⁵
- The discontinuance rate was reported as 56% in this study, with thrombocytopenia being the principal reason for stopping therapy.⁵ Within the group of patients who had received a prior radioimmunoconjugate (12%), two-thirds were discontinued from therapy because of severe thrombocytopenia; however, a high percentage (88%) of these patients responded to bendamustine.⁵ Grade 3/4 neutropenia and thrombocytopenia were reported in 54% of patients (with 5 episodes of febrile/neutropenia) and 25% of patients, respectively.⁵

Discussion:

Background:

Preliminary results from the StiL study comparing the BR regimen with R-CHOP as first-line therapy for advanced-stage indolent NHL have shown similar response rates across all histology subtypes.¹ Based on Kaplan-Meier survival curve estimates, the overall survival (OS) for all patients, reported as an aggregate, was similar for both groups, approximating a 2-year OS of 90%.¹ The incidence of leukopenia and infectious complications was higher in the R-CHOP arm; however, additional details are needed to fully evaluate the clinical importance of these data, especially in elderly patients.⁸ The investigators state that 66% of the patients enrolled in this study were 60 years of age or older, suggesting that both regimens may be safe and effective in elderly NHL patients.¹ However, full statistical analysis has not yet been performed as part of this interim analysis.¹

The ORR rates for both R-CHOP (96%) and BR (88%) as first-line therapy for mantle cell lymphoma in the StiL study¹ are comparable to the results previously reported in a phase II study using R-CHOP exclusively in mantle cell patients (96%).⁶ In that study, the PFS rates were similar for R-CHOP in patients with or without a molecular remission (16.5 and 18.8 months, respectively).⁶ PFS has not yet been reported for the subset of mantle cell patients treated with BR in the StiL study.¹ Although there is no standard induction regimen for the treatment of mantle cell lymphoma, the use of a combination chemoimmunotherapy regimen or an autologous stem-cell transplant may be considered as treatment options.⁷ However, the use of intensive regimens may be limited to younger, fit patients because of the high toxicity profile of such regimens.⁷ Therefore, additional data are needed from the ongoing StiL trial to establish the role of BR as a potential first-line regimen, especially in elderly mantle cell patients.⁸

An *in vitro* study, comparing the pharmacologic effects of bendamustine in non-Hodgkin lymphoma cells demonstrated a distinctly different cytotoxicity pattern compared with other structurally related (alkylator) compounds.⁹ The results from this study suggest that bendamustine produces its cytotoxic effects via activation of the p53-dependent stress pathway, resulting in a strong activation of intrinsic apoptosis; additionally, bendamustine inhibits several mitotic checkpoints, producing a ‘mitotic catastrophe’ phenomenon characterized by increased death of damaged cells as they enter into mitosis.⁹ Lastly, unlike some other alkylating agents, bendamustine appears to activate different DNA repair pathways, which may result in less susceptibility to drug resistance.⁹ These properties of bendamustine may in part explain the effectiveness in drug-resistant cells and the activity in NHL patients with refractory disease.⁹ Results from 2 studies suggest that BR has activity in relapsed/refractory indolent NHL, as indicated by high ORR rates and a durable PFS of 23–24 months in patients with or without prior rituximab exposure.^{2,3} Although response rates were lower for patients who had received a prior rituximab-containing regimen, the duration of response was similar to that of the overall study population; for patients who had received 2 or more prior chemotherapy regimens, there was a small difference in the duration of response compared with the remainder of the study group.³ No

patients who had received radioimmunotherapy were enrolled in either of these two studies;^{2,3} therefore, the safety of bendamustine-rituximab following prior treatment with an anti-CD20 radioimmunoconjugate is not fully established.⁸ The median PFS for both studies is reported as an aggregate; therefore, specific survival data is not known for patients based on their level of pretreatment (i.e., number of prior regimens), prior exposure to rituximab, and characteristics of their disease (e.g., sensitive or refractory to their last treatment).^{2,3} Current treatment options for relapsed/refractory indolent NHL may include the use of maintenance rituximab, purine analog-based therapies, anti-CD20 radioimmunoconjugates, and stem-cell transplantation.¹⁰ Although not directly compared in a randomized trial, the median PFS reported with the BR regimen in these 2 studies is longer than the estimated PFS reported of 16 months with the salvage regimen, rituximab-fludarabine-cyclophosphamide-mitoxantrone (R-FCM);¹¹ however, differences exist in the patient selection with regards to exposure to rituximab and the number of prior therapies, thereby limiting a direct comparison between these 2 regimens.^{2,3,8} Both iodine I 131 tositumomab (Bexxar) and yttrium Y 90 ibritumomab tiuxetan (Zevalin) are FDA-approved in relapsed/refractory NHL and two meta-analyses had reported long-term durable responses (i.e. defined as a time-to-progression of at least 12 months) in 32–37% of heavily treated low-grade or follicular lymphoma patients with a median number of 2 and 4 prior regimens, respectively.^{12,13} Achievement of a complete response predicts for a long-term response (LTR) with radioimmunotherapy.^{12,13} Therefore, additional data are needed to establish a correlation between response rates and the response duration following treatment with bendamustine-rituximab, since the goal of therapy is to improve the outcome in multiple-relapsed patients by increasing the ORR rate and inducing durable remissions.^{8,12}

Results from 2 trials with the BR regimen have shown high overall and complete response rates (ORR: 75–92%; CR: 50–42%) in patients with relapsed mantle cell lymphoma.^{2,3} Although not directly compared in a randomized trial, these data appear favorable compared with the PFS of 8 months reported with the R-FCM regimen¹¹ and also compared with a duration of response of 9.2 months reported with the FDA-approved regimen, bortezomib.¹⁵ The incidence of hematologic toxicity (e.g., neutropenia and thrombocytopenia) is similar between BR and these regimens;^{3,11} however, unlike with bortezomib, peripheral neuropathy has not been reported with the BR regimen.¹⁻⁵ Additional data are needed from comparative trials with larger sample sizes to fully establish the clinical benefit of BR in this setting.⁸

Results from 2 studies evaluating the use of single-agent bendamustine in patients with rituximab-refractory disease, a clinical scenario defined as failure to respond (i.e., failure to achieve at least a partial response) or disease progression within 6 months of therapy,⁵ have shown response rates of 75–77% in heavily treated patients who had received a mean number of 2 prior regimens.^{4,5} The median PFS has been reported as 7.1–9.3 months in these studies.^{4,5} Within these study populations, a shorter PFS was reported for patients who had evidence of disease transformation, patients who were refractory to their most recent regimen, and in patients with alkylator-sensitive disease.^{4,5} Favorable prognostic characteristics in this patient population include nontransformed disease and having received only 1 or 2 prior regimens.⁵ Grade 3/4 neutropenia and thrombocytopenia have been reported as 54–61% and 25%, respectively.^{4,5} Severe thrombocytopenia, requiring discontinuance of bendamustine in a large number of patients, has been reported in patients previously treated with a radioimmunoconjugate; yet, despite this toxicity, high rate of responses has been reported in this group of patients.⁵ The incidence of hematologic toxicity with bendamustine given as monotherapy is higher compared with the combination of bendamustine given with rituximab, presumably related to the use of higher doses (120 versus 90 mg) and its use in more heavily treated patients.⁵ Both iodine I 131 tositumomab (Bexxar) and yttrium Y 90 ibritumomab tiuxetan (Zevalin) are FDA-approved in rituximab-refractory indolent, follicular NHL, including in patients with disease transformation,¹⁵ and their use has resulted in a median time-to-progression of 6.8 months and a median PFS of 10.4 months, respectively;^{16,17} yet, a significantly improved PFS has been reported with ¹³¹I-tositumomab (Bexxar) in responding patients.¹⁷ Therefore, additional data are needed from future studies to characterize the durability of responses and to establish the benefit of bendamustine in this poor-prognosis population, especially considering patients who may not be candidates to receive radioimmunotherapy.⁸

Summary:

Bendamustine-rituximab appears to produce comparable response rates, resulting in a similar event-free survival rate relative to R-CHOP in advanced-stage indolent NHL, based on results from the initial interim analysis of the StiL study.¹ Additional data, however, are needed with long-term follow-up to fully characterize the survival rates in indolent NHL.⁸ Until those data are available, the use of bendamustine as first-line therapy in this patient population is not fully established at this time.⁸

High response rates have been reported in both arms of the StiL study for the subset of patients with mantle cell lymphoma.¹ However, EFS (i.e., progression and relapse-free survival) for the bendamustine-rituximab regimen has only been reported as an aggregate reflecting the entire study population of both indolent NHL and mantle cell patients.¹ Additional data are needed from a subset analysis with additional survival data (e.g., PFS), especially in elderly patients with mantle cell lymphoma, to compare the activity of bendamustine-rituximab with responses reported for current chemoimmunotherapy induction regimens used as first-line therapy.⁸ Until those data are available, the use of bendamustine-rituximab as first-line therapy for mantle cell lymphoma is not fully established at this time.⁸

The bendamustine-rituximab regimen is active in relapsed and refractory indolent NHL.^{2,3} Based on the favorable PFS data and side effect profile that appears comparable to that of another salvage regimen (e.g., R-FCM),¹¹ bendamustine-rituximab may be considered a reasonable choice for multiple-relapsed, refractory, nontransformed indolent NHL patients who have not received prior radioimmunotherapy, may have a contraindication to receiving either an anthracycline or a purine analog, or in whom it may not be feasible to use an anti-CD20 radioimmunoconjugate (i.e., a medical contraindication or an accessibility issue).⁸

Bendamustine-rituximab has demonstrated activity in a small number of patients with relapsed mantle cell lymphoma evidenced by an improved PFS and response duration,^{2,3} which compares favorably with the median PFS reported with existing therapies such as R-FCM and bortezomib;^{10,13} Additional data are needed with a larger sample size to confirm these improved responses.⁸ However, based on the improved PFS and response duration data, bendamustine-rituximab may be considered a reasonable choice for the treatment of relapsed mantle cell lymphoma.⁸

Bendamustine administered as monotherapy is active in rituximab-refractory indolent NHL, predominantly in patients with nontransformed or with sensitive disease characteristics.⁵ Therefore, bendamustine may be considered a reasonable choice for rituximab-refractory, indolent NHL;⁸ bendamustine may also be considered an alternative in patients who are not candidates for radioimmunotherapy due to either patient selection (i.e., a clinical contraindication) or accessibility issues.⁸

References:

1. Rummel MJ, von Gruenhagen U, Niederle N et al. Bendamustine plus rituximab versus CHOP plus rituximab in the first-line treatment of patients with indolent and mantle cell lymphomas: first interim results of a randomized phase III study of the Study Group Indolent Lymphomas, Germany. Proceedings of the 49th Annual Meeting of ASH, Atlanta, GA, 2007 Dec 8-11. Abstract No. 385.
2. 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.
3. 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.
4. Kahl B, Bartlett NL, Leonard JP et al. Bendamustine is safe and effective in patients with rituximab-refractory, indolent B-cell non-Hodgkin's lymphoma. Proceedings of the 49th Annual Meeting of ASH, Atlanta, GA, 2007 Dec 8-11. Abstract No. 1351.
5. Friedberg JW, Cohen PC, Chen L et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J Clin Oncol.* 2008. 26:204-10.
6. Howard OR, Gribben JG, Neuberger DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. *J Clin Oncol.* 2002;20:1288-94.
7. Kahl BS. New therapeutic strategies for mantle cell lymphoma. In: ASCO 2008 Educational Book. 2008:392-7.
8. AHFS Oncology Expert Committee reviewer's comments (personal observations).
9. Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Trenda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents *Clin Cancer Res.* 2008; 14:309-17.
10. Indolent, recurrent adult non-Hodgkin lymphoma. From: PDQ. Physician data query (database). Bethesda, MD: National Cancer Institute; 2008 Oct 20.
11. Forspointner R, Dreyling M, Repp R, et al The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German low-grade lymphoma study group. *Blood.* 2004; 104:3064-71.

12. Fisher RI, Kaminski MS, Wahl RL et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol.* 2005; 23:7565-73
13. Witzig TE, Molina A, Gordon I et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with Yttrium 90 ibritumomab tiuxetan. *Cancer.* 2007;109:1804-10.
14. Fisher RI, Bernstein SH, Kahl BS et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2006;24:4867-74.
15. Leonard JP, Gregory SA, Maloney DG et al. Optimizing the treatment of patients with rituximab-pretreated recurrent indolent non-Hodgkin lymphoma. *Clin Adv Hem Oncol.* 2008; 6:437-45.
16. Witzig TE, Flinn IW, Gordon LI et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol.* 2005; 23:7565-73.
17. Horning SJ, Younes A, Jain V et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol.* 2005;23:712-9.