

2. INTRODUCTION

2.3 Overview

Non-Hodgkin's Lymphoma (NHL) is a cancer of the cells of the lymphatic system. There are many different types of NHL which can be divided into aggressive (fast-growing) and indolent (slow-growing) types. Prognosis and treatment depend on the stage and type of disease. The anti-CD20 monoclonal antibody is a standard treatment in various stages of indolent NHL. Combination chemotherapy has been the standard first-line treatment option for NHL for many years, and the alkylating agent cyclophosphamide is a mainstay in these combinations. Rituximab is approved for use in combination with CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy in the first-line setting. Rituximab, as monotherapy or in combination with chemotherapy, is also a standard treatment for patients with relapsed NHL. Once disease is refractory to rituximab therapy, however, treatment choices are limited.

Bendamustine is a cytotoxic compound that was initially synthesized in 1963 in the German Democratic Republic and is approved for marketing in Germany for the treatment of patients with chronic lymphocytic leukemia (CLL), Hodgkin's disease, NHL, and multiple myeloma.

The sponsor is seeking approval of bendamustine hydrochloride (HCL) for injection for the treatment of indolent B-cell NHL for patients who have progressed during or following treatment with rituximab or a rituximab-containing regimen. The primary study being used to support this NDA is study SDX-105-03, a single-arm, multi-center study in approximately 100 patients with indolent B-cell NHL who are refractory to rituximab. A Phase II study (SDX-105-01) with a similar design was also being used to support this NDA. Both trials enrolled patients in the US and Canada.

A previous NDA for bendamustine was submitted on September 19, 2007 for the indication of CLL (NDA #22-249). It was approved on March 20, 2008, during the review for the current NDA. Quality and non-clinical information for this NDA are cross-referenced to NDA 22-249.

2.2 Data Sources

The submission exists on the EDR under the following network path:

\\fdswa150\nonectd\N22303\N_000\2007-12-28

The data sets for the studies included in the submission exist in the following network path:

\\fdswa150\nonectd\N22303\N_000\2007-12-28\crt\datasets\

Additional raw data was submitted after the original submission. These data exist in the following network path:

\\FdsWa150\nonectd\N22303\N_000\2008-01-17\other\Raw Data\

3. STATISTICAL EVALUATION

The focus of this review is on trial SDX-105-03, which underwent a Special Protocol Assessment by the FDA. Study SDX-105-01 is being used to evaluate the consistency of the results from study SDX-105-03. The primary difference between the two studies is that 1) SDX-105-01 included patients with transformed B-cell NHL and 2) SDX-105-01 did not use an independent review committee (IRC) for the evaluation of radiology scans. In order to enhance the comparison of results between the two studies, the subgroup of patients from SDX-105-01 who had transformed B-cell NHL has been excluded.

A third study, SDX-105-02, is a single-arm, multicenter study that evaluated the safety and activity of bendamustine in combination with rituximab in patients with relapsed indolent or mantle cell NHL. Since this study was not specific to the indication being sought, results were not evaluated for this review.

3.1 Evaluation of Efficacy

3.1.1 Study Design and Objectives

Study SDX-105-03

Study SDX-105-03 is a single-arm study conducted in approximately 100 patients across 28 centers in the US and Canada with indolent B-cell NHL who had progressed during or following treatment with rituximab or a rituximab-containing regimen. Patients were to be treated with bendamustine HCL at 120 mg/m² administered by IV infusion over 60 minutes at single doses, repeated every 3 weeks on days 1 and 2. Treatment was to include at least six and at most eight 3-week cycles followed by an end-of-treatment evaluation within 28 days of the last dose of study drug. Dose reductions were allowed for patients who experienced grade 3 or 4 nonhematologic or grade 4 hematologic toxicity. Patient accrual started in October, 2005 and the data cutoff date for the final report was July 16, 2007.

The primary objective of the study was to describe the overall response rate (ORR) and duration of response (DR) to a regimen of bendamustine in patients with rituximab-refractory indolent NHL. The secondary efficacy objective was to assess the duration of progression-free survival (PFS). Other secondary objectives of the study relate to assessments of safety and pharmacokinetic parameters.

Study SDX-105-01

Study SDX-105-01 is a Phase II single-arm study that was designed using the Simon two-stage method with an initial, Stage I enrollment of 22 patients. If there were at least 6 responses, then an additional 50 patients were to be enrolled into Stage II for a total of 72 patients. If less than 6 responses were noted among the first 22 patients, then a response rate of less than 20% was to be assumed and the study was to be stopped.

Other aspects of the design were very similar to that of Study SDX-105-03. The dose and treatment regimens were identical, as were the rules for dose reductions, although patients in

Study SDX-105-01 were allowed to stay on treatment for a maximum of 12 cycles, compared to 8 in study SDX-105-03. The primary difference with respect to the patient population is that study SDX-105-01 allowed patients with transformed B-cell NHL to enroll in the trial whereas study SDX-105-03 did not.

Reviewer's Note:

In settings where there is no available therapy and where major tumor regressions can be presumed to be attributed to the tested drug, ORR and DR observed in single-arm studies may be considered as evidence to support drug approval. In the setting of NHL patients who are refractory to rituximab or a rituximab-containing regimen, treatment options are limited and these single-arm trials can be considered. This judgment is however deferred to the clinical review team.

3.1.2 Study Assessments and Endpoints

Assessments for study SDX-105-03 were provided by investigators and the IRC. Assessments by the IRC were considered primary. An IRC was not used in study SDX-105-01.

Disease Status

Disease status and tumor responses were assessed on Day 42 \pm 3 days, Day 84 \pm 3 days, and Day 168 \pm 3 days (if needed). Disease status was classified as one of the following:

- Complete response (CR)
- Complete response/unconfirmed (CRu)
- Partial response (PR)
- Stable disease (SD)
- Relapsed disease (RD)
- Progressive disease (PD)
- Unknown (evaluation incomplete) (UE)

Criteria for each of these classifications are based on a modified version of the International Workshop Response Criteria (IWRC) for NHL. Explicit criteria and modifications are provided in the Appendix (Section 6). Table 1 provides a summary of the criteria.

Table 1: Summary of Response Criteria for NHL

| <i>Response Category</i> | <i>Physical Examination</i> | <i>Lymph Nodes</i> | <i>Lymph Node Masses</i> | <i>Bone Marrow</i> |
|--------------------------|-----------------------------------|--------------------|--------------------------|-------------------------|
| CR | Normal | Normal | Normal | Normal |
| CRu | Normal | Normal | Normal | Indeterminate |
| | Normal | Normal | >75% decrease | Normal or indeterminate |
| PR | Normal | Normal | Normal | Positive |
| | Normal | ≥50% decrease | ≥50% decrease | Irrelevant |
| | Decrease in liver/spleen | ≥50% decrease | ≥50% decrease | Irrelevant |
| Relapse/progression | Enlarging liver/spleen; new sites | New or increased | New or increased | Reappearance |

Note: See the Appendix for definitions of “normal” and “indeterminate”.

Overall Response Rate and Duration of Response

The ORR is defined as the proportion of patients who achieve a best response of CR, CRu, or PR during the study. DR was calculated for patients with a response of CR, CRu, or PR and was defined as the time interval from the date of first documentation of the response to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first. For patients who did not die, progress, or change therapies due to progression, the end of the time interval was censored at the date of the last assessment where a patient was alive and had an assessment where there was no evidence of progression. This included assessments with an un-evaluable (UE) outcome.

Progression-Free Survival (PFS)

PFS was determined for all patients and was defined as the time interval from the date of the first bendamustine dose to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first. For patients who did not die, progress, or change therapies due to progression, the time of progression was censored at the date of the last assessment where a patient was alive and had an assessment where there was no evidence of progression. This included assessments with a UE outcome.

Reviewer’s Note:

Because of the variability in the natural history of the disease, single arm trials can not characterize time-to-event endpoints such as PFS. These can only be properly assessed in randomized trials. As a result, PFS results will receive limited attention in this review.

Sensitivity Analyses

Sensitivity analyses were conducted in order to assess the sensitivity of the results to the rules used to define DR and PFS event and censoring dates. For these analyses, assessments with outcomes of UE were not considered when determining the date of the last adequate assessment where a death, progression, or a change of therapy due to progression was *not* observed. For cases where PD was observed but at an assessment that was late by more than 50% of the

timeframe allowed by the protocol, the date of progression was assigned to the date of the assessment that immediately preceded the late assessment where PD was observed.

3.1.3 Statistical Methodologies

Results presented in this review were derived by the reviewer using the data provided by the sponsor and the methodologies described below, unless specified otherwise. Results from study SDX-105-01 are based on the updated addendum data, rather than those used for the original study report.

3.1.3.1 Primary Analysis

The primary endpoints for study SDX-105-03 are ORR and DR using IRC assessments. The primary null hypothesis relating to ORR is that the response rate for patients who receive bendamustine treatment is $\leq 40\%$. The alternate hypothesis is that the ORR is $>40\%$. The null hypothesis was to be tested using the lower limit of a 95% exact confidence interval (CI) around the estimated ORR.

The null hypothesis for DR was to test that the median DR is ≤ 4 months vs. the alternate hypothesis that the median DR is >4 months. Median DR was to be calculated using the Kaplan-Meier method. The null hypothesis was to be tested using the lower limit of the 95% CI using the nonparametric method of Brookmeyer and Crowley.

The overall Type I error rate of 5% was protected from multiple comparisons by only claiming statistical significance for DR if the test for ORR was also significant.

The primary analysis set (PAS) used for the primary analyses consisted of all study patients who received study drug, regardless of whether or not they met all inclusion/exclusion criteria.

Reviewer's Note:

Statistical inferences involving historical controls or arbitrary cut-points are not meaningful or necessary in this setting for single-arm trials. P-values will therefore not be reported in this review, although 95% confidence intervals will be. It should also be noted that DRs can only be evaluated in the subgroup of patients who respond.

3.1.3.2 Secondary Analyses

The secondary efficacy endpoint for study SDX-105-03 is PFS. Median PFS was calculated using the Kaplan-Meier method. A 95% CI around the median PFS estimate was calculated using the nonparametric method of Brookmeyer and Crowley.

3.1.3.3 Sensitivity and Exploratory Analyses

The statistical methodology used for the sensitivity analyses matched that used for the corresponding primary analyses.

Exploratory analyses were conducted in order to test the consistency of the results across various subgroups. These subgroups are displayed in Table 2. For ORR, the sponsor used logistic

regression to model the subgroup factors. For DR and PFS, the sponsor used Cox proportional hazard (PH) regression to model the subgroup factors.

Table 2: Subgroups Used in Exploratory Analyses

| <i>Subgroup Characteristic</i> | <i>Subgroup categories</i> |
|--------------------------------------|--|
| Number of prior chemotherapy courses | ≤3 vs >3 |
| Prior alkylator therapy exposure | Yes vs no (alkylator therapies defined by a medical expert). |
| Prior radioimmunotherapy exposure | Yes vs no |
| Chemotherapy disease status | Refractory vs sensitive to last prior chemotherapy regimen (refractory defined as a best response of stable disease or progressive disease; sensitive defined as a best response of complete response or partial response) |
| Alkylator therapy disease status | Refractory vs sensitive to last prior alkylator therapy (refractory defined as a best response of stable disease or progressive disease; sensitive defined as a best response of complete response or partial response) |
| FLIPI | 4 or less vs more than 4 nodal areas |
| FLIPI Risk Category | Low risk, intermediate risk, high risk |
| Bulky disease at baseline | Low vs high bulk (≥10 cm) |

Reviewer’s Notes

Prior to amending the SAP, the number of prior chemotherapy courses was divided by (b) (4) [redacted]. This was changed to ≤3 vs. >3 as shown in Table 2. The sponsor’s reason for the change stated that the initial subgroups were “not considered clinically relevant”. In order to create subgroups with adequate sample size, this reviewer used the initial cut-points of (b) (4) [redacted] and alternative cut-points of <3 vs. ≥3.

Symptomatic status as determined by the B symptoms for the Ann Arbor staging system was also used as a subgroup by this reviewer. Symptoms were either fever (>38° C), drenching night sweats, or weight loss more than 10% of body weight. Other subgroups, including those based on race, gender, age, and country were considered as well.

Subgroup analysis results appear in Section 4. The logistic regression and Cox PH models identified above as exploratory subgroup analyses were not considered for this review.

3.1.4 Efficacy Results and Conclusions

3.1.4.1 Patient Disposition, Demographics, and Baseline Characteristics

A total of 100 patients were enrolled and treated across 28 sites in study SDX-105-03. A total of 61 patients with indolent NHL were enrolled and treated across 14 sites in study SDX-105-01. Nine investigators were involved in both trials.

Table 3 contains a summary of patient disposition for the two trials. Two patients enrolled into study SDX-105-03 were later found to be ineligible and were therefore never treated, leaving 100 patients who were treated and were evaluable for safety and efficacy. One patient who enrolled into study SDX-105-01 was never treated due to the suspicion of a central nervous system disease, leaving 61 patients with indolent NHL who received treatment and were evaluable for efficacy. The additional 15 patients enrolled into study SDX-105-01 with non-indolent, transformed disease were all treated and evaluable for safety.

Patients in both studies were to complete a minimum of 6 cycles of study drug.

**Table 3: Patient Disposition in Studies SDX-105-03 and SDX-105-01
(All Enrolled Patients)**

| Status | Study | |
|--|-----------------------|-----------------------|
| | SDX-105-03 n/N (%) | SDX-105-01 n/N (%) |
| Enrolled | 102/102 (100) | 62/62 (100) |
| Treated | 100/102 (98.0) | 61/62 (98.4) |
| Completed 6 cycles of Treatment | 60/100 (60.0) | 30/61 (49.2) |
| Early Discontinuation (prior to 6 cycles) | 40/100 (40.0) | 31/61 (50.8) |
| Reasons for Early Discontinuation | | |
| Adverse Event | 27/100 (27.0) | 18/61 (29.5) |
| Consent Withdrawn (Not due to AE) | 1/100 (1.0) | 0/61 (0.0) |
| Disease Progression | 10/100 (10.0) | 9/61 (14.8) |
| Other | 2/100 (2.0) | 4/61 (6.6) |
| Treatment Discontinuation after >=6 cycles | 18/60 (30.0) | 10/30 (33.3) |
| Reasons for Treatment Termination after >=6 cycles | | |
| Adverse Event | 1/60 (1.7) | 4/30 (13.3) |
| Consent Withdrawn (Not due to AE) | 1/60 (1.7) | 0/30 (0.0) |
| Disease Progression | 1/60 (1.7) | 4/30 (13.3) |
| Received Maximum Benefit from Therapy | 13/60 (21.7) | 0/30 (0.0) |
| Other | 2/60 (3.3) | 2/30 (6.7) |

[†] Includes subjects with indolent NHL only.

Patients in study SDX-105-03 were allowed to receive a maximum of 8 cycles of study drug whereas patients in study SDX-105-01 were allowed to receive a maximum of 12 cycles. This is likely to explain the differences between studies in the reasons for termination after 6 or more cycles. Patients in SDX-105-01 were allowed to be treated longer and therefore counted as early terminators if they stopped treatment prior to receiving 12 cycles.

Patient demographics are summarized in Table 4. In study SDX-105-03, the majority of the patients were male (65%) and white (88%). The average age was 59 years and 30% of the

patients were elderly (≥ 65 years). The average body mass index (BMI) was 29 kg/m². Eighty-eight percent of the patients were enrolled at sites in the US.

Overall, the demographic profile of non-indolent NHL patients in study SDX-105-01 was similar, although there was a smaller proportion of males (57%) and a higher proportion of elderly patients (41%) in study SDX-105-01.

Table 4: Patient Demographics in Studies SDX-105-03 and SDX-105-01 (All Treated Patients)

| Characteristic | Study | |
|---|------------------------|-----------------------|
| | SDX-105-03 (N=100) | SDX-105-011 (N=61) |
| Gender [n/N (%)] | | |
| Male | 65/100 (65.0) | 35/61 (57.4) |
| Female | 35/100 (35.0) | 26/61 (42.6) |
| Race [n/N (%)] | | |
| White | 88/100 (88.0) | 53/61 (86.9) |
| Black | 7/100 (7.0) | 5/61 (8.2) |
| Asian | 1/100 (1.0) | 0/61 (0.0) |
| Other | 4/100 (4.0) | 3/61 (4.9) |
| Age (years) | | |
| Mean \pm SD (N) | 59.3 \pm 10.60 (100) | 62.0 \pm 12.64 (61) |
| Median (Range) | 60.0 (31.0 - 84.0) | 62.0 (38.0 - 84.0) |
| Elderly [n/N (%)] | | |
| Non-elderly (<65 years of age) | 70/100 (70.0) | 36/61 (59.0) |
| Elderly (≥ 65 years of age) | 30/100 (30.0) | 25/61 (41.0) |
| Body Mass Index (kg/m²) | | |
| Mean \pm SD (N) | 29.3 \pm 6.26 (99) | 28.8 \pm 7.02 (61) |
| Median (Range) | 29.0 (18.2 - 54.7) | 27.5 (18.0 - 52.4) |
| Country of Investigative Site | | |
| Canada | 12/100 (12.0) | 8/61 (13.1) |
| United States | 88/100 (88.0) | 53/61 (86.9) |

[†] Includes patients with indolent NHL only.

Baseline characteristics are summarized in Table 5. In study SDX-105-03, 90% of patients did not have bulky disease (defined as having a node with a diameter of at least 10cm at baseline), 84.5% did not present B symptoms (based on the Ann Arbor staging system for lymphoma) at baseline, 91% were previously treated with alkylator therapy, and 76% had no prior radioimmunotherapy exposure. The distribution of patients across the other subgroups was more even. Bulky disease and prior radioimmunotherapy use was not collected in study SDX-105-01. Based on the other baseline characteristics, however, the sub-population of patients with indolent NHL in study SDX-105-01 was generally similar to the population studied in SDX-105-03.

**Table 5: Baseline Characteristics in Studies SDX-105-03 and SDX-105-01
(All Treated Patients)**

| Characteristic | Study | |
|---|-----------------------|-----------------------|
| | SDX-105-03 (N=100) | SDX-105-011 (N=61) |
| Bulky Disease [node(s)≥10cm] | | |
| No | 90/100 (90.0) | NA |
| Yes | 10/100 (10.0) | NA |
| Disease Stage | | |
| Stage I | 8/100 (8.0) | |
| Stage II | 16/100 (16.0) | 8/61 (13.1) |
| Stage III | 33/100 (33.0) | 20/61 (32.8) |
| Stage IV | 43/100 (43.0) | 33/61 (54.1) |
| B Symptom status | | |
| Asymptomatic | 84/100 (84.0) | 54/61 (88.5) |
| Symptomatic | 16/100 (16.0) | 7/61 (11.5) |
| Prior alkylator therapy | | |
| No | 9/100 (9.0) | 12/61 (19.7) |
| Yes | 91/100 (91.0) | 49/61 (80.3) |
| Prior alkylator result | | |
| Refractory | 30/81 (37.0) | 19/46 (41.3) |
| Sensitive | 51/81 (63.0) | 27/46 (58.7) |
| Number of prior chemotherapy courses | | |
| 0 | 1/100 (1.0) | 5/61 (8.2) |
| 1 | 41/100 (41.0) | 30/61 (49.2) |
| 2 | 36/100 (36.0) | 19/61 (31.1) |
| 3 | 14/100 (14.0) | 7/61 (11.5) |
| 4+ | 8/100 (8.0) | 0/61 (0.0) |
| Prior chemotherapy result | | |
| Refractory | 36/87 (41.4) | 18/51 (35.3) |
| Sensitive | 51/87 (58.6) | 33/51 (64.7) |
| Prior radioimmunotherapy use | | |
| No | 76/100 (76.0) | NA |
| Yes | 24/100 (24.0) | NA |
| FLIPI score | | |
| Mean±SD (N) | 2.0 ± 1.12 (62) | 2.2 ± 1.14 (41) |
| Median (Range) | 2.0 (0.0 - 5.0) | 2.0 (0.0 - 4.0) |
| FLIPI risk | | |
| High risk | 18/62 (29.0) | 15/41 (36.6) |
| Intermediate risk | 26/62 (41.9) | 14/41 (34.1) |
| Low risk | 18/62 (29.0) | 12/41 (29.3) |
| Lymph node involvement | | |
| > 4 | 48/100 (48.0) | 24/61 (39.3) |
| ≤4 | 52/100 (52.0) | 37/61 (60.7) |

[†] Includes patients with indolent NHL only.