

The protocol for Study SDX-105-03 underwent a Special Protocol Assessment by the FDA. There were 4 series of amendments. The first three were implemented before the first patient was enrolled. According to the sponsor, the 4<sup>th</sup> and final amendment was implemented after agreement regarding the definition of the patient population from FDA and after 35 patients had been enrolled. The primary purpose of this amendment was to alter the definition of rituximab refractory so that patients who only received rituximab as part of their treatment with ZEVALIN<sup>®</sup> were eligible. The evaluation of efficacy from this study is based on data available up to and including July 15, 2007. This cut-off date was chosen to allow for 6 months of follow-up among all treated patients.

Study SDX-105-01 is a Phase II trial with a similar design and patient population to that of SDX-105-03. The primary differences between the two studies are that 1) SDX-105-01 included patients with transformed B-cell NHL and 2) SDX-105-01 did not use an IRC for the evaluation of radiology scans. This review was therefore focused on the results of study SDX-105-03. Results from SDX-105-01, excluding patients with transformed B-cell NHL, were used to evaluate the consistency of the results.

### **5.1 Statistical Issues and Collective Evidence**

1. Although double-blind, randomized trials are generally preferred, objective endpoints in single-arm trials may be considered for approval in an oncology setting where treatment options are limited. In treating NHL patients who are refractory to rituximab or a rituximab-containing regimen, major tumor regressions can be presumed to be attributable to the test drug. Evidence of sufficiently high objective response rates along with durable response durations can be considered as the basis for regulatory approval in this clinical setting.
2. Statistical inferences involving historical controls or arbitrary cut-points are not meaningful or reliable in single-arm trials. Results from inferential analyses are therefore not reported in this review, although 95% confidence intervals are.
3. During the review of study SDX-105-03 by the clinical reviewer, two discrepancies with the IRC response assessments were noted between the data sets, data listings, and the study report results. After confirmation from the sponsor (via an e-mail sent on July 28, 2008), the following changes were made for this reviewer's analyses:
  - The best response for Patient 65036 was changed from a CR to a CRu in order to reflect the final decision by the IRC's oncologist adjudicator
  - The best response for Patient 24093 was changed from a PR to an SD since the PR response occurred 2 days after the data cut-off date of July 15, 2007

As a result of these changes, the ORR based on the IRC assessments (the primary endpoint) comes to 74% (95% CI: 64.3%, 82.3%). The median duration of response is 40 weeks (95% CI: 30.3, 46.9). The CR rate was reduced from 14% as reported by the applicant to 13%.

4. The primary IRC results in study SDX-105-03 are similar to those obtained from the investigator assessments of response. Using the investigator assessments, the ORR is 80% (95% CI: 70.8, 87.3) and the median duration of response is 39 weeks (95% CI: 33.7, 60.1).
5. The data are further supported by results from Study SDX-105-01, a Phase II study with a similar design and patient population to that of SDX-105-03. When considering only those patients in SDX-105-01 who had indolent NHL, the ORR is 79% (95% CI: 66.3, 88.1) and the median duration of response is 39 weeks (95% CI: 26.6, 72.6).
6. Results are generally similar across various subgroups defined by demographic and baseline characteristics. A possible exception is with regards to subgroups based on prior alkylator and chemotherapy response status. Response rates are lower among patients who are refractory to prior alkylator therapies (60% ORR) and refractory to prior chemotherapies (61% ORR), compared to those who are sensitive to prior alkylator therapies (86% ORR) and sensitive to prior chemotherapies (88% ORR). In both groups, refractory patients experienced shorter DRs compared to sensitive patients (33 weeks vs. 42 weeks, respectively, for prior alkylator therapy patients and 27 weeks vs. 43 weeks, respectively, for prior chemotherapy patients).

Table 13 provides point estimates and 95% CIs for ORRs and median DRs for studies SDX-105-03 and SDX-105-01.

**Table 13: Summary of Overall Response Rates and Response Durations (Studies SDX-105-03 and SDX-105-01)**

Study	Assessor	N	CR+CRu+PR		Response Duration	
			Events	95% CI	Median (weeks)	95% CI
SDX-105-03	IRC	100	74 (74%)	(64.3, 82.3)	40.1	(30.3, 46.9)
	Investigator	100	80 (80%)	(70.8, 87.3)	39.4	(33.7, 60.1)
SDX-105-01 <sup>1</sup>	Investigator	61	48 (79%)	(66.3, 88.1)	39.3	(26.6, 72.6)

<sup>1</sup>Includes patients with indolent NHL only.

## 5.2 Conclusions and Recommendations

The sponsor is seeking approval of bendamustine HCL for injection for the treatment of indolent B-cell NHL among patients who have progressed during or following treatment with rituximab or a rituximab-containing regimen. They are claiming that effectiveness has been demonstrated by the two single-arm studies SDX-105-03 and SDX-105-01. Because these are single-arm studies, no statistical inferences are being drawn from them in this review. Rather, the emphasis is on the rate and duration of responses.

Based on this reviewer's analysis of the IRC assessments in study SDX-105-03, 74 out of 100 patients (74%) achieved a best response of PR, CRu, or CR (95% CI: 64.3%, 82.3%). These results differ from those of the sponsor due to a correction to the status of Patient 24093 whose best response was changed from a PR to a SD since the PR response occurred 2 days after the

data cut-off date of July 15, 2007. The recalculated median DR is 40 weeks (95% CI: 30.3, 46.9). These results are generally consistent with those based on investigator assessments and with those from the subset of patients in study SDX-105-01 who had indolent NHL. Subgroup analyses mostly revealed consistent results between subgroups based on demographic and baseline characteristics, although effectiveness was somewhat diminished among patients who were refractory to prior alkylator therapies and prior chemotherapies.

Whether the effectiveness is adequate for approval of bendamustine for the proposed indication will be determined by clinical judgment and an assessment of the product's overall risk/benefit profile.

## 6. APPENDIX

### Modified International Workshop Response Criteria (IWRC) for NHL

#### **Complete Response (CR) requires the following:**

1. Complete disappearance of all detectable clinical and radiologic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (eg, lactate dehydrogenase [LDH]) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size ( $\leq 1.5$  cm in their greatest transverse diameter for nodes  $> 1.5$  cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to  $\leq 1$  cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate ( $\geq 20$  mm biopsy core).

#### **Complete Response/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one of more of the following features:**

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

#### **Partial Response requires the following:**

1.  $\geq 50\%$  decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should

include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, *e.g.*, large-cell lymphoma or low-grade lymphoma (*i.e.*, small, lymphocytic small cleaved, or mixed small cleaved, or mixed small and large cells).
6. No new sites of disease.

**Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).**

**Relapsed disease (CR, CRu) requires the following:**

1. Appearance of any new lesion or increase by  $\geq 50\%$  in the size of previously involved sites.
2.  $\geq 50\%$  increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

**Progressive disease (PR, nonresponders) requires the following:**

1.  $\geq 50\%$  increase from nadir in the PD (Product of Diameters for a **single** lesion) of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

## 7. SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: P. Chris Holland, M.S.

Date: September 25, 2008

Concurring Reviewer(s): Rajeshwari Sridhara, Ph.D., Team Leader, Deputy Division  
Director

Aloka Chakravarty, Ph.D., Division Director

cc:

HFD-150/M. Vialpando

HFD-150/V. Kwitkowski

HFD-150/A. Ibrahim

HFD-711/P.C. Holland

HFD-711/R. Sridhara

HFD-711/A. Chakravarty

HFD-700/R. Tiwari

HFD-700/E. Nevius

C:\Projects\Treanda\statistical-review-treanda-nda22303.doc

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Peter Holland  
9/25/2008 03:37:55 PM  
BIOMETRICS

Rajeshwari Sridhara  
9/25/2008 04:48:47 PM  
BIOMETRICS

Aloka Chakravarty  
9/26/2008 08:55:34 AM  
BIOMETRICS