

3.1.4.2 Primary and Secondary Endpoints

3.1.4.2.1 Study SDX-105-03

3.1.4.2.1.1 Objective Response Rates and Response Duration

The ORR and 95% CI for the IRC and investigator assessments are summarized in Table 6. Assessments from the IRC are considered primary. According to IRC assessments, 74 (74%) patients achieved a PR or better compared to 80 (80%) based on investigator assessments. Thirteen patients (13.0%) achieved a CR and 4 (4.0%) achieved a CRu according to the IRC. Based on investigator assessments, 22 patients (22.0%) achieved a CR and 5 patients (5.0%) achieved a CRu. There were 9 patients who were considered responders by the investigators but not by the IRC and 3 patients considered responders by the IRC, but not by the investigators, resulting in 88 of 100 patients for whom there was agreement between the IRC and PI with respect to best response status.

Reviewer's Note:

During the review by the clinical reviewer, Virginia Kwitkowski, two discrepancies between the data sets, data listings, and the study report results were noted with regard to the IRC response assessments. 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*

Results in this review reflect these changes and therefore do not match the sponsor's results.

Table 6: Response Rates¹ in Study SDX-105-03 (All Treated Patients)

Assessor	Response Category ¹	% (n/N)	95% CI ²
IRC (Primary)	ORR (CR, CRu, or PR)	74.0 (74/100)	(64.3, 82.3)
	CR	13.0 (13/100)	
	CRu	4.0 (4/100)	
	PR	57.0 (57/100)	
	SD	17.0 (17/100)	
	PD	7.0 (7/100)	
	UE/missing	2.0 (2/100)	
	Investigator (Secondary)	ORR (CR, CRu, or PR)	
CR		22.0 (22/100)	
CRu		5.0 (5/100)	
PR		53.0 (53/100)	
SD		13.0 (13/100)	
PD		6.0 (6/100)	
UE/missing		1.0 (1/100)	

¹ CR=complete response, CRu=unconfirmed complete response, PR=partial response,

SD=stable disease, PD=progressive disease, UE/missing=unable to evaluate or missing.

² Confidence intervals calculated using exact binomial probabilities.

Figure 1 displays the DR based on both IRC and investigator assessments. Kaplan-Meier methods are used to estimate the probability of a continued response over time.

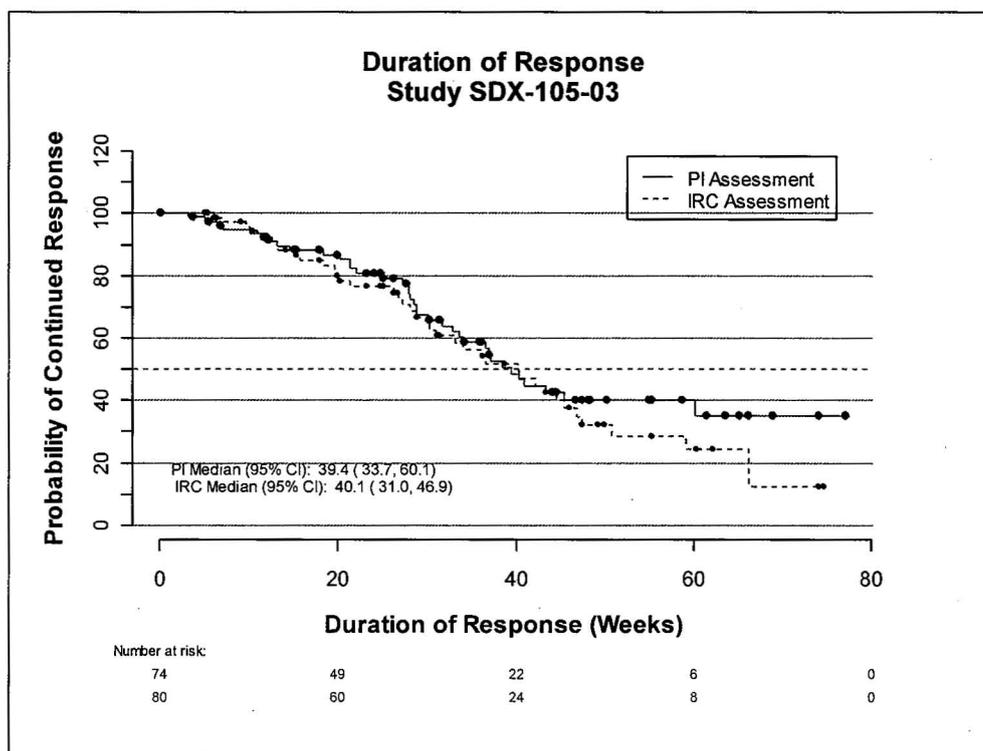


Figure 1: Duration of Response, Study SDX-105-03 (IRC and PI Responders)

Table 7 displays the median DR and 95% CIs around the estimates. The median DR was 40 weeks using the IRC assessments (95% CI: 30.3, 46.9) and 39 weeks using the investigator assessments (95% CI: 33.7, 60.1). Sensitivity analysis results were very similar. The median duration of response using sensitivity censoring criteria was also 40 weeks (95% CI: 31.0, 46.9).

Table 7: Median Response Duration in Study SDX-105-03 (All Treated Patients)

Assessor	N	Events	Censored	Median Response Duration (weeks)	95% CI
IRC (Primary)	74	39 (53%)	35 (47%)	40.14	(30.29, 46.86)
Investigator (Secondary)	80	37 (46%)	43 (54%)	39.43	(33.71, 60.14)

Figure 2 displays the DR based on IRC assessments for patients who achieved a best response of CR or CRu and for patients who achieved a best response of PR (not for comparison). The median DR for CR+CRu responders was 45.3 weeks (95% CI: 40.3, 59.1). The median DR for PR responders was 36.1 weeks (95% CI: 27.3, 46.9)

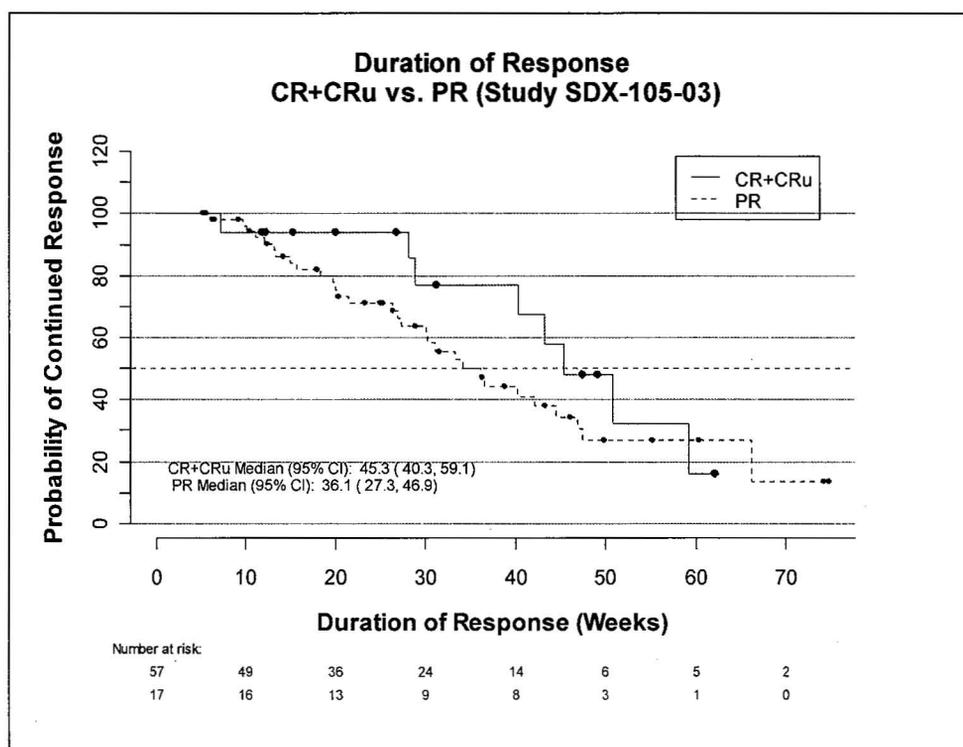


Figure 2: Duration of Response, CR+CRu vs. PR (Study SDX-105-03 IRC Responders)

3.1.4.2.1.2 Progression Free Survival

Table 8 summarizes the results from the analyses of PFS using investigator and IRC progression data provided by the sponsor. The median PFS based on the IRC assessments is 40.3 weeks (95% CI: 35.0, 51.9). The median PFS based on the PI assessments is 42.4 weeks (95% CI: 35.0, 51.9).

Table 8: Median Progression-Free Survival

Outcome	N	Events	Censored	Median Progression-Free Survival (weeks)	95% CI
PFS (PI Assessment)	100	54 (54%)	46 (46%)	42.4	(35.0, 51.9)
PFS (IRC Assessment)	100	57 (57%)	43 (43%)	40.3	(35.0, 51.9)

Results from the sensitivity analysis of PFS based on IRC assessments are very similar. The median PFS time using the sensitivity rules is 39.0 weeks (95% CI: 34.7, 51.1).

3.1.4.2.2 Study SDX-105-01

3.1.4.2.2.1 Objective Response Rates and Response Duration

An IRC was not employed for response assessments in Study SDX-105-01, which might be expected in a proof-of-concept, phase II study. Excluding the patients with transformed disease, 48 of the 61 treated patients (78.7%) achieved at least a partial response in this study. Eleven patients (18.0%) achieved a CR and twelve (19.7%) achieved a CRu. Table 9 displays the ORR and 95% CIs for Study SDX-105-01 and Study SDX-105-03 for comparison.

Table 9: Response Rates¹ in Studies SDX-105-03 and SDX-105-01 (All Treated Patients)

Study	Response Category ²	ORR % (n/N)	95% CI ³
SDX-105-01	ORR (CR, CRu, or PR)	78.7 (48/61)	(66.3, 88.1)
	CR	18.0 (11/61)	
	CRu	19.7 (12/61)	
	PR	41.0 (25/61)	
	SD	3.3 (2/61)	
	PD	14.8 (9/61)	
	UE/missing	3.3 (2/61)	
SDX-105-03	ORR (CR, CRu, or PR)	80.0 (80/100)	(70.8, 87.3)
	CR	22.0 (22/100)	
	CRu	5.0 (5/100)	
	PR	53.0 (53/100)	
	SD	13.0 (13/100)	
	PD	6.0 (6/100)	
	UE/missing	1.0 (1/100)	

¹ Based on investigator assessments.

² CR=complete response, CRu=unconfirmed complete response, PR=partial response
SD=stable disease, PD=progressive disease, UE/missing=unable to evaluate or missing.

³ Confidence intervals calculated using exact binomial probabilities.

Figure 3 displays DRs based on investigator assessments for Study SDX-105-01. Results from Study SDX-105-03 are also shown in order to assess consistency between the studies. Kaplan-Meier methods are used to estimate the probability of a continued response over time.

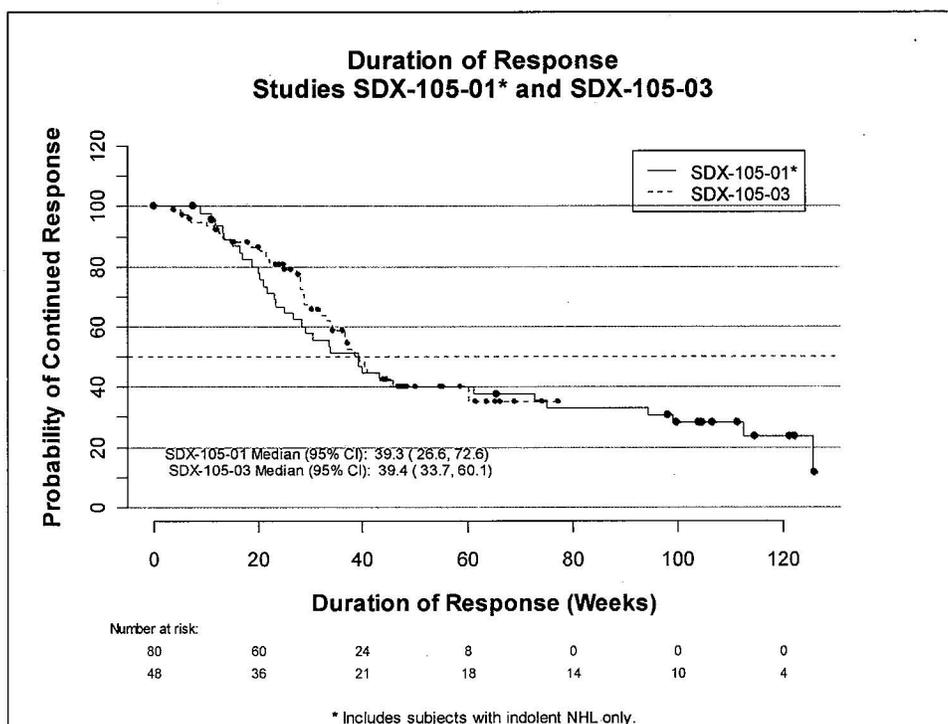


Figure 3: Duration of Response, Studies SDX-105-01 and SDX-105-03 (PI Responders)

Table 10 displays the median DR and 95% CIs around the estimates. The median DR was 39 weeks in both studies.

Table 10: Median Response Duration in Study SDX-105-01 and SDX-105-03 (PI Responders)

Assessor	N	Events	Censored	Median Response Duration (weeks)	95% CI
SDX-105-01 ¹	48	29 (60%)	19 (40%)	39.3	(26.6, 72.6)
SDX-105-03 ²	80	37 (46%)	43 (54%)	39.4	(33.7, 60.1)

¹Includes responders with indolent NHL only.

²Based on investigator assessments.

3.1.4.2.2.2 Progression Free Survival

Table 11 summarizes the results from the analyses of PFS using investigator progression data for patients with indolent NHL in study SDX-105-01. Results from PI assessments in study SDX-105-03 are displayed for comparison. The median PFS in study SDX-105-01 is 35.9 weeks (95% CI: 28.7, 49.0). These results are lower compared to those from study SDX-105-03, where the median PFS based on investigator assessments is 42.4 weeks (95% CI: 35.0, 51.9).

Table 11: Median Progression-Free Survival¹ (Studies SDX-105-01 and SDX-105-03)

Study	N	Events	Censored	Median Progression-Free Survival (weeks)	95% CI
SDX-105-01 ²	61	41 (67%)	21 (33%)	35.9	(28.7, 49.0)
SDX-105-03	100	54 (54%)	46 (46%)	42.4	(35.0, 51.9)

¹Based on investigator assessments.

²Includes patients with indolent NHL only.

3.1.4.3 Conclusions

Using corrected IRC assessments, 74% of patients in study SDX-105-03 achieved a best response of PR or better (95% CI: 64.3, 82.3). These patients achieved a median DR of 40 weeks (95% CI: 30.3, 46.9). A higher rate of response was noted by the investigators (80%), but with a similar median DR (39 weeks). Overall, there was 88% concurrence between the IRC and PIs with respect to patients' best response status. Results in study SDX-105-01, a phase II study with a similar patient population and study design, were similar (ORR=78%, DR=39 weeks). The primary results therefore appear to be consistent across studies and only slightly sensitive to reader variability.

3.2 Evaluation of Safety

Please refer to the Clinical Review of this application for the evaluation of safety. Additionally, since the studies in this submission were also submitted for safety evaluation in NDA 22,249, the Clinical Review for that submission may also be of interest.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup evaluations are divided into demographic subgroups and baseline characteristic subgroups and are described in the corresponding sections below.

4.1 Gender, Race, Age, and Geographic Region

Figure 4 displays a forest plot of ORRs and the associated 95% confidence intervals for demographic subgroups defined by gender, race, age group (<65 years of age and ≥65 years of age), and geographic region (United States vs. Canada). Note that the vertical reference line at 40% is based on a cut-point used by the sponsor, but is not being used in this review to suggest statistical significance. In general, rates are consistent across subgroups. Confidence intervals are wide for the smaller subgroups of non-Whites and patients who were treated at Canadian sites, both of which had 8 responders out of 12 patients. The 67% response rates are not largely out of line with the opposite group and would, in fact, equal the rates for the corresponding opposite group if one additional patient were to have responded.

IRC Objective Response Rates by Demographic Subgroups Study SDX-105-03

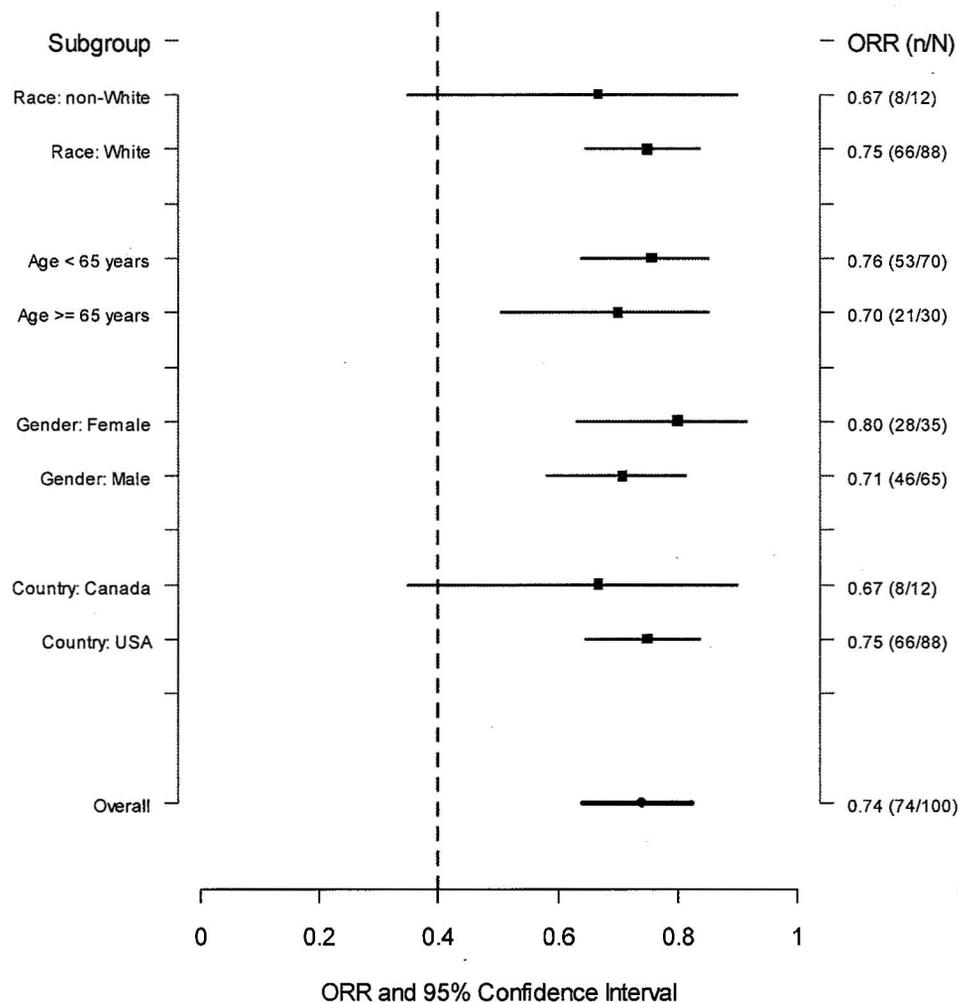


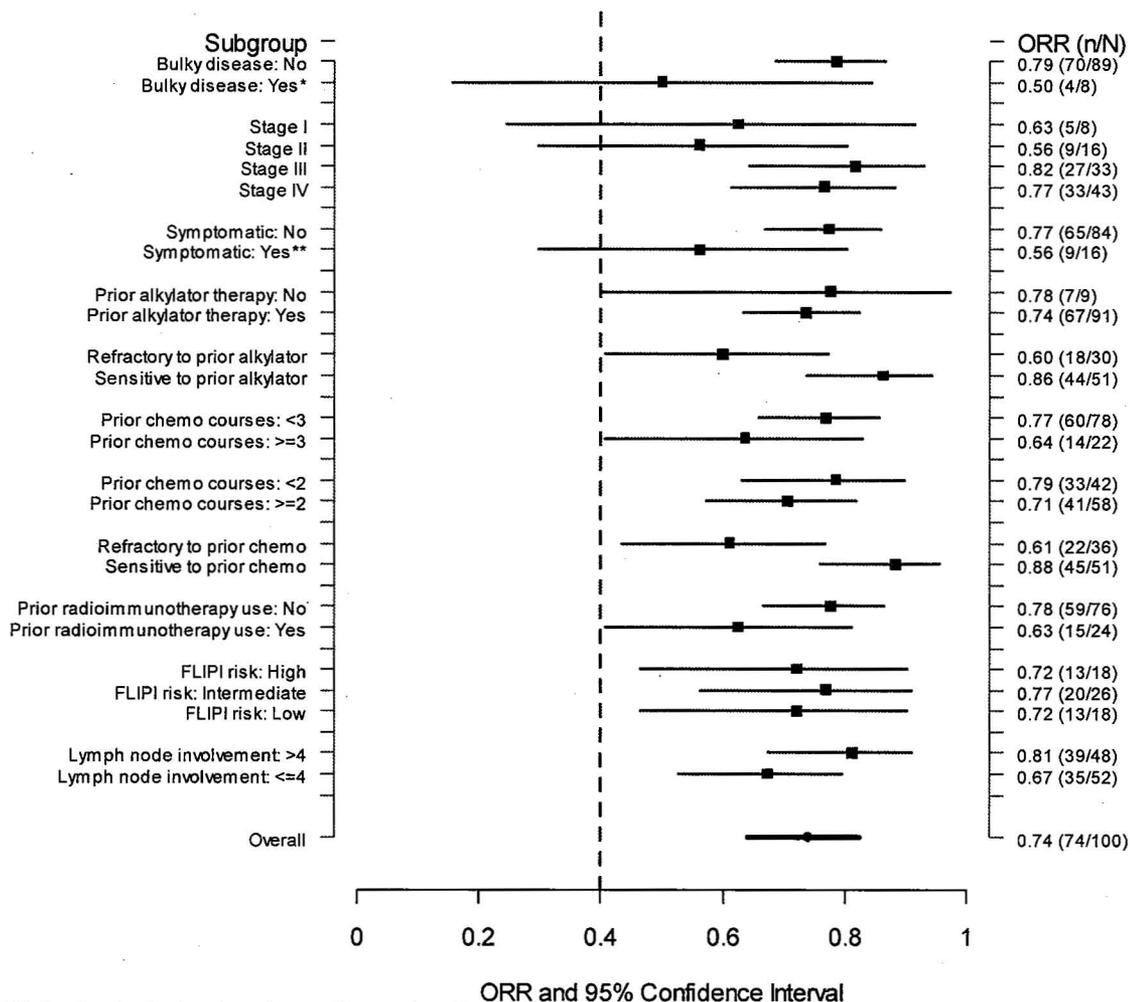
Figure 4: IRC Objective Response Rates by Demographic Subgroups (Study SDX-105-03)

4.2 Other Special/Subgroup Populations

The baseline characteristics described in Table 2 and summarized in Table 5 were used to make comparisons across subgroups with respect to the ORRs, as shown in Figure 5. Many of these were groups defined by the sponsor, used in the clinical study report, and provided in the submitted data sets. One exception is the symptomatic subgroup, which was derived from the B symptom data collected as part of the Ann Arbor staging system for lymphoma. For subgroups

based on prior chemotherapy courses, the sponsor's original SAP used <2 and ≥ 2 to define the two groups. This was later changed to ≤ 3 and >3 because, according to the amended SAP, subgroups based on (b) (4) were "not considered clinically relevant". However, since only 8 patients had more than 3 prior chemotherapy courses, cut-points used by this reviewer include (b) (4) (the original cut-points) and <3 vs. ≥ 3 .

IRC Objective Response Rates by Baseline Characteristic Subgroups Study SDX-105-03



* Defined as having lymph nodes ≥ 10 cm at baseline

** Based on Ann Arbor staging B symptoms

Figure 5: IRC Objective Response Rates by Baseline Characteristic (Study SDX-105-03)

The lowest ORR resulted from the bulky disease group, where 4 out of 8 patients (50%) responded. The second lowest ORR was in the symptomatic group, where 9 out of 16 patients

(56%) responded. These two groups, however, represent 2 of the smallest 3 subgroups and have wide confidence intervals with upper bounds that exceed the point estimates for their opposing groups.

The two opposing subgroups with the smallest amount of overlap between their respective 95% CIs are the groups based on prior chemotherapy status and prior alkylator therapy status. For patients who were refractory to chemotherapy, the ORR is 61% (95% CI: 43.4, 76.9) compared to 88% (95% CI: 76.1, 95.6) for patients who were sensitive to prior chemotherapy. Similarly, patients who were refractory to prior alkylator therapy have an ORR of 60% (95% CI: 40.6, 77.3) compared to 86% (95% CI: 73.7, 94.3) for patients who were sensitive to prior alkylator therapy. Note that, as shown in Table 2, sensitive is defined as a best response of complete response or partial response; refractory is defined as a best response of stable disease or progressive disease. Patients who have an unknown or missing response to their prior therapy or who never received the prior therapy are not included in these subgroups.

Median DRs for these subgroups appear in Table 12. For patients refractory to alkylator therapies, the median DR is approximately 9 weeks shorter compared to those sensitive to alkylator therapies (33 weeks vs. 42 weeks). For patients refractory to chemotherapies, the median DR is approximately 16 weeks shorter compared to those sensitive to chemotherapies (27 weeks vs. 43 weeks).

Table 12: Median Response Duration for Prior Therapy Subgroups (IRC Responders with Prior Exposure to Respective Therapy)

Prior Therapy	Status	N	Events	Censored	Median Response Duration (weeks)	95% CI
Alkylator	Refractory	18	11 (61%)	7 (39%)	33.29	(21.43, NE)
	Sensitive	44	21 (48%)	23 (52%)	42.14	(36.14, 50.71)
Chemotherapy	Refractory	22	13 (59%)	9 (41%)	27.29	(21.43, NE)
	Sensitive	45	22 (49%)	23 (51%)	43.29	(36.57, 50.71)

NE = Not estimable.

5. SUMMARY AND CONCLUSIONS

The sponsor submitted NDA 22,303 to support the 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. At the time of submission, bendamustine was under review at FDA for the treatment of patients with CLL. It was approved for CLL on March 20, 2008.

To support the NHL indication, results from two single-arm, multicenter studies were submitted. 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.