

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125388Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA Serial Number:** 125388.0

**Drug Name:** Brentuxumab Vedotin (SGN-35)

**Indication(s):** Hodgkin's Lymphoma

**Applicant:** Seattle Genetics, Inc.

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**Biometrics Division:** Division of Biometrics V

**Statistical Reviewer:** Kyung Yul Lee, Ph.D., Statistical Reviewer

**Concurring Reviewers:** Mark Rothmann, Ph.D., Lead Mathematical Statistician  
Rajeshwari Sridhara, Ph.D., Division Director

**Medical Division:** Division of Hematology Products

**Clinical Team:** Dr. De Claro, Clinical Reviewer  
Dr. Kwitkowski, Clinical Team Leader

**Project Manager:** MS. Akinsanya

**Keywords:** Hodgkin' lymphoma, single arm, Phase 2 study, objective response

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## 1. EXECUTIVE SUMMARY

This submission consists of the results of the study, SG035-0003 which is a Phase 2, multicenter, single arm trial to determine the antitumor efficacy of single agent brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL) following autologous stem cell transplant. The dose and schedule is 1.8 mg/kg as a single outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity a minimum of 8 to 16 cycles. The study was conducted by US, Canada, and Western Europe investigators. The primary objective of this study was to determine the antitumor efficacy of single-agent SGN-35 as measured by the overall objective response rate (CR+PR) assessed by independent review facility (IRF). The secondary objectives were to estimate the duration of response, progression-free survival, overall survival and to assess safety, tolerability and pharmacokinetics.

The observed primary endpoint of objective response rate (ORR) was 73% and the secondary endpoint of the complete response rate (CR) was 32% by FDA analysis. The FDA analysis of duration of responses for median objective response and median complete response durations were 6.7 months and 20.5 months, respectively. These results were similar to the applicant's results. Based on these observed overall objective response, complete response and duration of responses reasonably likely predict clinical benefit in patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant.

An advisory committee meeting for oncology drug products was held on July 14, 2011 for BLA submissions, 125388/0(SG035-0003) and 125399/0 (SG035-0004). For both applications, the advisory committee voted unanimously (10-0) for accelerated approval. They are concerned about lack of long-term safety information and the limitation of risk-benefit determination.

The key statistical issues and findings that impact them, with regards to the demonstration of efficacy are summarized as follows:

- The applicant's objective and complete response rates by IRF were 75% and 34%, respectively. The applicant's objective response (OR) and complete remission (CR) rates by investigators' assessments were 72% and 33%, respectively. These results were similar to FDA's OR and CR rates of 73% and 32%, respectively.
- The exact concordance rate between the investigators' assessments and IRF was 42.2%. There were 52% agreements for ORR between the IRF assessments and the investigators' assessments. There were two positron emission tomography (PET) scan positive patients in the CR among 61 PET scan positive patients in the applicant's analysis.
- The median duration of the applicant's objective response was 6.7 months based on IRF (42 progressive disease (PD) out of 76 ORR) with 95% CI of (3.7, 12.0) and 10.9 months based on the investigators' assessment (36 PD out of 73 ORR) with 95% CI of (7.1, NE). The median duration of OR for the investigators' assessments was 3.2 months longer than that of IRF.

- The FDA median duration of ORR based on the updated data with cutoff date of March 4, 2011 was 6.7 months (95% CI: 4.0, 14.8) with 46 events among 74 OR patients. The median duration of complete remission was 20.5 months (95% CI: 12.0, NE) with 12 events among 33 CR patients. The median duration of partial remission (PR) was 3.5 months (95% CI: 2.2, 4.1) with 34 events among 41 PR patients.

As this is a single arm study, caution should be taken when interpreting the results of progression-free survival and overall survival analyses.

- The progression-free-survival (PFS) analyses by IRF and by investigators' assessments were performed with the updated dataset. Based on IRF, 69 patients (67.6%) had either disease progression or died among 102 ITT patients. The median PFS by IRF was 5.6 months with 95% CI of (5.0, 9.0). Based on investigators' assessments, 65 patients (63.7%) had either progressive diseases or death. The median PFS by investigators' assessments was 9.3 months with 95% CI of (7.1, 12.2).
- The overall survival analysis was performed with updated dataset. There were 28 deaths (27.5%) among 102 ITT patients based on March 4, 2011 data cutoff date. The median duration of OS was 22.4 months with 95% CI of (21.7, NE).

## 2. INTRODUCTION

### 2.1 Overview

SGN-35 is an antibody-drug conjugate (ADC) directed against the CD30 antigen and is to treat patients with CD30-positive hematologic malignancies such as Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL) which are the most common CD30-positive malignancies.

Study SG035-0003 was sponsored by Seattle Genetics, Inc. (Bothell, WA) and conducted by US, Canada, and Western Europe investigators enrolling at least one patient in a total of 25 sites: 19 sites in the US, 3 sites in France, 2 sites in Canada, and 1 site in Italy.

The dose was 1.8 mg/kg as a single outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Patients who achieved stable disease or better as assessed by investigator were to receive a minimum of 8, but no more than 16 cycles of study treatment.

The primary objective was to determine the antitumor efficacy of single-agent SGN-35 as measured by the overall objective response rate in patients with relapsed or refractory Hodgkin lymphoma following autologous stem cell transplant.

The secondary objectives were to assess duration of tumor control, including duration of response and progression-free survival, survival, the safety, tolerability and the pharmacokinetics of SGN-35.

## **2.2 Data Sources**

The data format was SDTM and ADaM datasets were provided. The locations of the data are as follows;

Study Report: \\cber-fs3\\cber-fs3\m\CTD\_Submissions\STN125388\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\hodgkin\5352-stud-rep-uncontr\sg035-0003

SDTM: \\cber-fs3\m\CTD\_Submissions\STN125388\0000\m5\datasets\sg035-0003\tabulations

ADaM: \\cber-fs3\m\CTD\_Submissions\STN125388\0000\m5\datasets\sg035-0003\analysis

## **3. STATISTICAL EVALUATION**

### **3.1 Data and Analysis Quality**

The quality and integrity of the submitted data were reviewed:

- It was possible to reproduce the primary analysis dataset from tabulation or SDTM datasets
- The derived dataset included most of important demographic variables. The reviewer did not need to merge too many datasets to generate variables.

### **3.2 Evaluation of Efficacy**

The Study SG035-0003 was the study that evaluated the efficacy of SGN-35 for the treatment of HL. This review focuses on the study of SG-035-003 for SGN-35 which was conducted in relapsed or refractory HL after autologous stem cell transplant.

#### **3.2.1 Study Design and Endpoints**

Study SG035-0003 is a phase 2, single-arm, international study designed to evaluate the efficacy and safety of SGN-35 in the treatment of patients with relapsed or refractory histologically-confirmed CD30-positive HL by central review. Patients previously received an autologous stem cell transplant (ASCT) at least 12 weeks (3 months) and completed any prior treatments

such as radiation, chemotherapy, biologics, and/or other investigational agents at least 4 weeks prior to the first dose of SGN-35. Patients must have completed any prior immunotherapy (e.g., rituximab) or radioisotopic therapy at least 12 weeks prior to the first dose of SGN35 in the absence of clear disease progression. The study was conducted at 25 sites in US, Canada, and Western Europe. Patients were to receive 1.8 mg/kg as a single outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Patients who achieved stable disease or better as assessed by investigator were to receive a minimum of 8, but no more than 16 cycles of study treatment.

The primary endpoint was the overall objective response rate per an independent review facility (IRF).

The secondary endpoints were;

- Response durability per IRF
- Complete remission (CR) rate per IRF
- Progression-free survival (PFS) per IRF
- Overall survival
- Type, incidence, severity, seriousness, and relatedness of adverse events, and laboratory abnormalities
- Population estimates of selected pharmacokinetics parameters

The additional endpoints were event-free survival, B-symptom resolution rate, and plasma cytokines or soluble CD30 (sCD30) levels that may be associated with outcome.

Anticancer activity measures were assessed using the revised response criteria for malignant lymphoma (Cheson et al 2007). An Independent Data Monitoring Committee (IDMC) monitored on a periodic basis the safety of patients participating in this trial.

Computed tomography (CT) scans (chest, neck, abdomen, and pelvis) were to be performed at baseline and Cycles 2, 4, 7, 10, 13, and 16 and positron emission tomography (PET) scans were to be done at baseline and Cycles 4 and 7. After discontinuing treatment, patients were to be followed for survival and disease status every 12 weeks until death or study closure. Patients who discontinued study with stable disease or better were to have CT scans done every 12 weeks until disease progression or relapse. Patients were to have an end of treatment (EOT) assessments 30 ± 7 days after receiving their final dose.

### **3.2.2 Patient Disposition, Demographic and Baseline Characteristics**

Among 123 screened patients, 102 patients were enrolled at 25 study centers; 19 sites in the United States, 3 sites in France, 2 sites in Canada, and 1 site in Italy. Twenty one patients were failed for screening. The majority of these patients did not meet one of the eligibility criteria (17 of 21; 81%).

All 102 patients (ITT population) enrolled on the study received at least one dose of SGN-35. The primary data cutoff date was August 4, 2010. The patient disposition is summarized in Table 1.

**Table 1 : Patient Disposition**

Disposition	ITT Population (N=102) n (%)
Completed 16 Cycles	18 (17.6)
Discontinued before 16 cycles	84 (82.4)
Progressive Disease	45 (44.1)
Adverse Event	20 (19.6)
Physician Decision	12 (11.8)
Withdrawal by Patient	7 (6.9)
Entered Long-term follow-up	99 (97.1)
Remained in the Long-term	85 (83.3)
Discontinued in the long-term	14 (13.7)
Death	12 (11.8)
Withdrawal by Patient	1 (1.0)
Lost to follow-up	1 (1.0)

Eighteen patients (17.6%) completed the maximum 16 cycles of treatment and 84 patients discontinued treatment fewer than 16 cycles; 45 patients due to disease progression (44.1%), 20 patients due to adverse events (19.6%), 12 patients (11.8%) due to investigator decision (11.8%), or 7 patients due to patient decision (6.9%). Seven patients received an allogeneic stem cell transplant as their first therapy subsequent to treatment with SGN-35.

A total of 17 patients are no longer in active follow up; 13 patients had died; an additional 2 patients had progressive disease and decided not to return for follow-up visits; 1 patient withdrew consent for additional follow-up assessments, and 1 patient was lost to follow up.

The efficacy analyses were based on the intent-to-treat (ITT) analysis set, defined as all 102 patients enrolled in the study. Patient demographics are summarized based on ITT population in Table 2.

**Table 2 : Patient Demographics**

	ITT Population (N=102) n, (%)
Age	
15-29	46 (45.1)
30-44	40 (39.2)
45-59	12 (11.8)
≥ 60	4 (3.9)
Median	31.0
Min, Max	15, 77

Gender	
Female	54 (52.9)
Male	48 (47.1)
Race	
White	89 (87.3)
Asian	7 (6.9)
Black	5 (4.9)
Other	1 (1.0)
ECOG	
0	42 (41.2)
1	60 (58.8)

The median age was 31 years with range of 15 to 77. The majority of patients were White (87.3%). There were more female (52.9%) than male patients (47.1%). The baseline ECOG performance score were 0 (41%) or 1 (59%).

All 102 patients were confirmed the diagnosis of CD30-positive HL by central pathology review.

The baseline disease characteristics are summarized in Table 3.

**Table 3 : Baseline Disease Characteristics**

ITT Population (N=102)	
n, (%)	
Disease Stage	
I	4 (3.9)
II	47 (46.1)
III	27 (26.5)
IV	20 (19.6)
Unknown	4 (3.9)
Disease Status	
Relapse	59 (57.8)
Refractory	43 (42.2)
B symptom (Cycle 1 Day 1)	
Yes	35 (34.3)
No	67 (65.7)
Primary Refractory Disease	72 (70.6)
Bone marrow Lymphoma Involvement, n (%)	8 (7.8)
Time from HL to 1 <sup>st</sup> Dose (Months)	
Median (Min, Max)	39.9 (11.8, 219.7)

There were 47 patients with Stage II HL at initial diagnosis (46.1%), 27 patients with Stage III (26.5%), 20 patients with Stage IV (19.65), 4 patients (4%) with Stage I, and 4 patients (54%) with unknown disease stage. The median time from initial HL diagnosis to the first dose of SGN-

35 was 39.9 months (range, 11.8 to 219.7). At baseline, 35 patients (34.3%) reported B symptoms and 8 patients (8%) had bone marrow lymphoma involvement.

The prior cancer-related therapies are summarized in Table 4.

**Table 4 : Prior Cancer-related Therapies**

	ITT Population (N=102) n, (%)
No. of Prior Cancer-related Radiotherapy	67 (65.7)
No. of Prior Cancer-related Systemic Therapy Median (Min, Max)	3.5 (1, 13)
No. of Prior Autologous Stem Cell Transplant	
1	91 (89.2)
2	11 (10.8)
HL Diagnosis to Most Recent ASCT(Months) Median (Min, Max)	17.9 (5, 115)
Most Recent ASCT to Relapse Post-ASCT (Months) Median (Min, Max)	6.7 (0, 131)
Most Recent ASCT to First Dose Median (Min, Max)	19.0 (3, 166)

Sixty seven patients (65.7%) had previously received cancer-related radiotherapy. The median number of prior cancer-related systemic therapies excluding autologous stem cell transplant was 3.5 (range, 1 to 13). All patients had received prior autologous stem cell transplant; 91 patients (89%) had received 1 prior transplant; 11 patients (11%) had received 2 prior transplants. The median time from initial HL diagnosis to the most recent autologous stem cell transplant was 17.9 months (range, 5 to 115) and the median time from the most recent autologous stem cell transplant to relapse post-transplant was 6.7 months (range, 0 to 131). The median time from the most recent autologous stem cell transplant to the first dose of SGN-35 was 19.0 months (range, 3 to 166 months).

### 3.2.3 Statistical Methodologies

#### Determination of Sample Size

The planned sample size was approximately 100 patients in this study. The null hypothesis was  $ORR < 20\%$  and alternative hypothesis was  $ORR \geq 20\%$ . With a sample size of 100, observing 29 (29%) objective responses (CR or PR) would allow to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 35%, the study would have approximately 90% power.

## **Statistical Methodology**

The intent-to-treat (ITT) analysis set included all patients enrolled in the study. The ITT analysis set was to be used for the efficacy endpoints analyses.

The per-protocol analysis set was defined as those patients who received at least one dose of SGN-35, had measurable disease at baseline, had the correct histological cancer type per central pathology review, and had no other major protocol deviations that could potentially affect tumor response. The per-protocol analysis set was to be used for secondary analyses of all efficacy endpoints.

The safety/modified intent-to-treat (mITT) analysis set included all patients who received at least one dose of SGN-35.

The objective response rate (ORR) was defined as the proportion of patients with complete remission (CR) or partial remission (PR) according to the revised response criteria for malignant lymphoma (Cheson et al. 2007). The ORR per IRF and its two-sided 95% exact confidence interval using the F distribution method given in Collett (1991) was calculated.

Duration of response was defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first subsequent documentation of objective tumor progression or to death due to any cause, whichever came first.

Progression-free survival (PFS) per IRF was defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever came first.

PFS was to be censored on the day following the date of the last radiological assessment of measured lesions documenting absence of progressive disease for patients who did not have objective tumor progression and were still on study at the time of an analysis, were given antitumor treatment other than the study treatment or the stem cell transplant, or were removed from study prior to documentation of objective tumor progression. Patients with lack of an evaluation of tumor response after their first dose were to have their event time censored at 1 day.

Duration of time to events was analyzed using Kaplan-Meier methodology. The median duration of response and its 95% CI was calculated using Brookmeyer and Crowley (1982).

### **3.2.4 Results and Conclusions**

#### **Primary Endpoint:**

The primary efficacy analysis was the ORR (Cheson 2007) as assessed by IRF based on ITT population. The applicant's primary endpoint results are summarized in Table 5.

**Table 5 : Applicant’s Primary Endpoint Results (ITT population)**

	ITT Population (N=102)
Objective Response (ORR)	76 (74.5%)
Complete Remission (CR)	35 (34.3%)
Partial Remission (PR)	41 (40.2%)
Exact 95% CI for ORR	(64.9, 82.6)
Exact 95% CI for CR	(25.2, 44.4)
Exact 95% CI for PR	(31.5, 49.4)

The applicant’s primary endpoint of objective response assessed by IRF was 76 patients out of 102 ITT patients (74.5%) with 95% CI of (64.9, 82.6). The complete remission was 35 patients (34.3%) and partial remission was 41 patients (40.2%).

*Reviewer’s comment;*

*The difference between IRF and the investigator’s assessments are summarized in Table 6.*

**Table 6 : Best Overall Responses Difference between IRF and Investigators’ assessments**

IRF PET \ Investigator	CR	PR	SD	PD	Total
CR	25 2	8 6	1 0	0 0	34 8
PR	7 3	28 25	4 4	0 0	39 32
SD	3 0	5 4	17 16	3 1	28 21
PD	0 0	0 0	0 0	0 0	0 0
Total	35 5	41 35	22 20	3 1	101 61

*The exact concordance rate between the investigators’ assessment and IRF was 43 out of 102 patients (42.2%). There were 53 patients’ agreement (52.0%) for CR and PR between the IRF assessments and the investigators’ assessments among 102 ITT populations.*

*The PET scan showed 61 patients had positive results. Two PET scan positive patients were categorized as CR in the applicant’s analysis. Dr. De Claro examined the best objective responses and changed the ORR for 6 patients. The patients’ ID numbers are as follows;*

- SG035-0003-11002-0086: Change CR to PR (FDA and Sponsor agree)*
- SG035-0003-10011-0074: Change CR to PR (Sponsor does not agree)*
- SG035-0003-10004-0019: Change PR to CR (FDA and Sponsor agree)*
- SG035-0003-10004-0042: Change CR to PR (FDA and Sponsor agree)*
- SG035-0003-10006-0047: Change PR to SD (IR sent to Sponsor)(NEW)*
- SG035-0003-39001-0070: Change PR to SD (IR sent to Sponsor)(NEW)*

The primary efficacy analysis results with ORR based on FDA evaluation are summarized in Table 7.

**Table 7 : FDA’s Primary Efficacy Results (ITT Population)**

	ITT Population (N=102)
Objective Response (ORR)	74 (72.5%)
Complete Remission (CR)	33 (32.4%)
Partial Remission (PR)	41 (40.2%)
Exact 95% CI for ORR	(63.9, 80.1)
Exact 95% CI for CR	(23.3, 42.3)
Exact 95% CI for PR	(31.5, 49.4)

The FDA primary endpoint of objective response per IRF was 74 patients out of 102 ITT patients (72.5%) with 95% CI of (63.9, 80.1). The complete remission was 33 patients (32.4%) and partial remission was 41 patients (40.2%).

Secondary Endpoints:

The secondary endpoints of applicant’s duration of responses are summarized in Table 8.

**Table 8 : Applicant’s Duration of Responses per IRF (ITT Population)**

	ITT Population (N=102)
Objective Response	76 (74.5%)
Number of Events	42 (41.2%)
PD	41 (40.2%)
Death	1 (1.0%)
Duration of ORR (Months)	
Median	6.7
95% CI	(3.7, 12.0)
Complete Response	35
Number of Events	12
PD	12
Death	0
Duration of CR (Months)	
Median	NE
95% CI	(8.8, NE)

Among 76 OR patients, 42 patients (55.3%) had progressive disease or death. The median duration of ORR was 6.7 months with 95% CI of (3.7, 12.0). Among 35 CR patients, 12 patients

(34.4%) had progressive disease. The median duration of CR was not reached with 95% CI of (8.8, NE).

The objective response and complete remission rates and the applicant's duration of responses for the investigators' assessment are summarized in Table 9.

**Table 9 : Applicant's Response Rates and Duration of Responses by Investigators' Assessments**

	ITT Population (N=102)
Objective Response Rate (ORR)	73 (71.6%)
Complete Remission (CR)	34 (33.3%)
Partial Remission (PR)	39 (38.2%)
Duration of ORR (Months)	
Median (95% CI)	10.9 (7.1, NE)
No. of Events	36
Duration of CR (Months)	NE
No. of Events	7

The objective response and complete remission rates based on the investigators' assessments were 71.6% and 33.3%, respectively. The median ORR was 10.9 months with 95% CI of (7.1, NE). The duration of complete remission for the investigators' assessments was not reached.

*Reviewer's comment:*

*The FDA's analysis results for the duration of responses are summarized in Table 10.*

**Table 10: FDA's Duration of Response per IRF**

	ITT Population (N=102)
Objective Response	74 (72.5%)
Number of Events	41 (40.2%)
PD	40 (39.2%)
Death	1 (1.0%)
Duration of ORR (Months)	
Median	6.7
95% CI	(4.0, 12.0)
Complete Response	33 (32.4%)
Number of Events	10 (9.8%)
PD	10
Death	0
Duration of CR (Months)	
Median	NE
95% CI	(6.9, NE)

Among 74 OR patients, 41 patients (55.4%) had progressive disease or death. The median duration of ORR was 6.7 months with 95% CI of (4.0, 12.0). Among 33 CR patients, 10 patients (30.3%) had progressive disease. The median duration of CR was not reached with the 95% CI of (6.9, NE).

The applicant's best overall responses are summarized in Table 11.

**Table 11: Applicant's Best Overall Responses**

	ITT Population (N=102)
<b>Best Response</b>	
Complete Remission (CR)	35 (34.3%)
Partial Remission (PR)	41 (40.2%)
Stable Disease (SD)	22 (21.6%)
Progressive Disease (PD)	3 (2.9%)
Not Evaluable (NE)	1 (1.0%)

The best clinical response per IRF was 35 CR patients (34.3%), 41 PR patients (40.2%), 22 SD patients (22%), and 3 PD patients (2.9%). One patient was not evaluable for responses.

*Reviewer's comment:*

*The FDA's best overall response results are summarized in Table 12.*

**Table 12: FDA's New Best Overall Responses**

	ITT Population (N=102)
<b>Best Response</b>	
Complete Remission (CR)	33 (32.4%)
Partial Remission (PR)	41 (40.2%)
Stable Disease (SD)	24 (23.5%)
Progressive Disease (PD)	3 (2.9%)
Not Evaluable (NE)	1 (1.0%)

*The FDA's best clinical response per IRF was 33 CR patients (32.4%), 41 PR patients (40.2%), 24 SD patients (23.5%), and 3 PD patients (2.9%).*

The secondary endpoint of progression-free survival analysis results are summarized in Table 13.

**Table 13: Applicant’s Progression-Free Survival per IRF and Investigators’ Assessments Results**

	ITT Population (N=102)	
	IRF	Investigator
PFS		
Number of Events	64 (62.7%)	57 (55.9%)
Duration of PFS (Months)		
Median	5.8	9.0
95% CI	(5.0, 9.0)	(7.1, 12.0)

Among ITT population of 102 patients, 64 patients (62.7%) have either had disease progression per IRF or died. The median PFS was 5.8 months with 95% CI of (5.0, 9.0). Fifty seven patients (55.9%) had disease progression or death by investigators’ assessments. The median PFS was 9.0 months with 95% CI of (7.1, 12.0).

*Reviewer’s Comments:*

*As this is a single arm study, caution should be taken when interpreting the results of progression-free survival and overall survival analyses. These results are exploratory sensitivity analyses.*

*Both the investigators’ assessments and IRF agreed that 51 patients (50.0%) were diagnosed as PD and 32 patients (31.4%) were not having PD. Six patients (5.9%) were diagnosed as PD by the investigators’ assessments, but were censored by IRF. Thirteen patients (12.7%) were diagnosed as PD by IRF, but were censored in the investigators’ assessments.*

*Among those 51 PD or death patients by both the investigators’ and the IRF determination, only 27 patients (52.9%) had the same PD or death dates, 4 patients’ PD or death dates (7.8%) were later in the investigators’ assessments than that of the IRF assessment and 20 patients’ PD or death dates (39.2%) were earlier in the investigators’ assessments than that of the IRF assessments.*

*There were total of 6 patients who were diagnosed as having PD based on the investigators’ assessments analysis, but were censored at the time of assessment based on the IRF analysis. The censoring is likely informative for these 6 patients. The results of the exploratory sensitivity analysis of the time to the first of PD by the investigators’ assessments or the IRF assessments are summarized in Table 14.*

**Table 14: Reviewer’s Sensitivity Analysis Results for First Time to PD between Investigators’ Assessments and IRF.**

	ITT Population (N=102)
Number of PD	70 (68.6%)
Time to PD (Months)	
Median (95% CI)	5.29 (4.83, 7.06)

*The exploratory analysis was performed by taking the first time to progression disease between the investigators’ assessments and the IRF assessments. In this analysis results showed that 70 patients out of 102 patients (71.5%) had PD or death. The estimated median PFS time was 5.29 months.*

The overall survival analysis results are summarized in Table 15.

**Table 15: Applicant’s Overall Survival Analysis Results**

	ITT Population (N=102)
OS	
Number of Events	13 (12.7%)
Duration of OS (Months)	
Median	NE
95% CI	(6.9, NE)

There were only 13 deaths (12.7%) among 102 ITT populations based on August 4, 2010 data cutoff date. The median duration of OS was not estimable.

*Reviewer’s comment:*

*As this is a single arm study, caution should be taken when interpreting the results of overall survival analyses. These are exploratory analyses results.*

*Lost to follow-up was examined by calculating difference between the cutoff date of August 4, 2010 and the censoring dates for censored patients based on the disease progressive assessment schedule of every 12 weeks. The time between censoring date and data cutoff date are summarized for CR ORR, PFS and OS in Table 16.*

**Table 16: Time between Censoring Date and the Data Cutoff Date for CR, ORR, PFS and OS Duration**

	≤12 weeks	13-24 weeks	25-36 weeks	>36 weeks
Duration of CR	1	13	5	4
Duration of ORR	9	15	3	7
Duration of PFS	22	6	2	8
Duration of OS	77	7	4	1

*There are 22 patients with complete responses and 25 patients with objective responses who missed their most recent disease assessments, 9 with complete responses (censored time  $\leq 7.9$  months) and 10 with objective responses (censored times  $\leq 7.5$ ) of which missed their two most recent disease assessments prior to the data cutoff date.*

*There are 16 patients with PFS and 12 patients with OS who missed their most recent disease assessments, 10 with PFS and 5 with OS of which missed their two most recent disease assessment prior to the data cutoff date.*

**Reviewer's Comments;**

*The applicant sent the updated efficacy data set based on cutoff date of March 4, 2011. The updated efficacy analysis results are summarized in Table 17.*

**Table 17: FDA Results for the Duration of Responses with Updated Datasets**

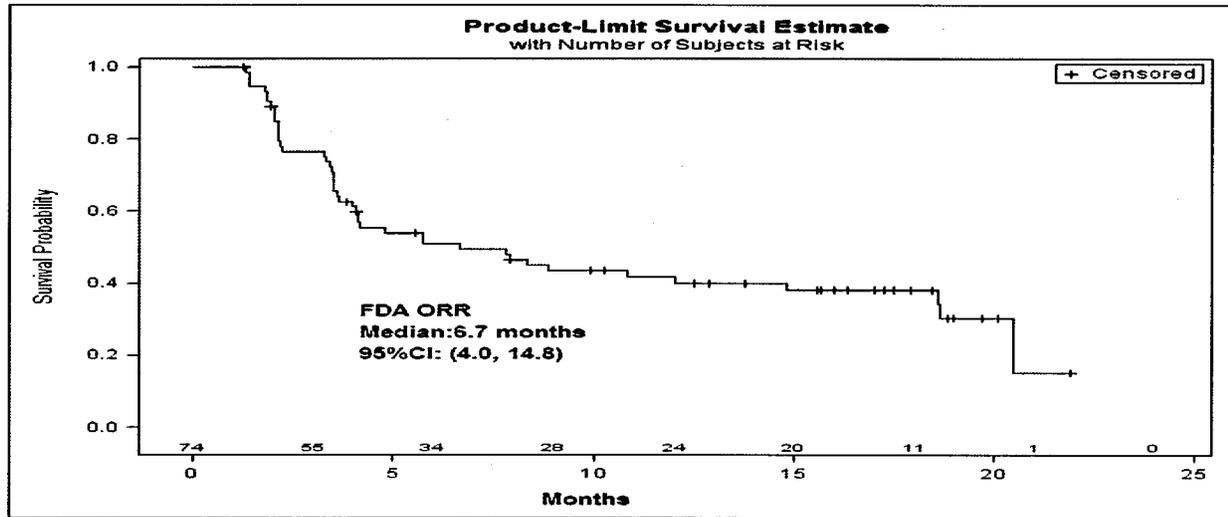
	ITT Population (N=102)
Complete Response	33 (32.3%)
Number of Events	12 (11.8%)
Duration of CR (Months)	
Median	20.5
95% CI	(12.0, NE)
Objective Response	74 (74.5%)
Number of Events	46 (46.1%)
Duration of ORR (Months)	
Median	6.7
95% CI	(4.0, 14.8)
Partial Response	41 (40.2%)
Number of Events	34 (33.3%)
Duration of PR (Months)	
Median	3.5
95% CI	(2.2, 4.1)

*Among 33 CR patients, 12 patients (36.4%) had progressive disease or death. The median duration of CR was 20.5 months with 95% CI of (12.0, NE).*

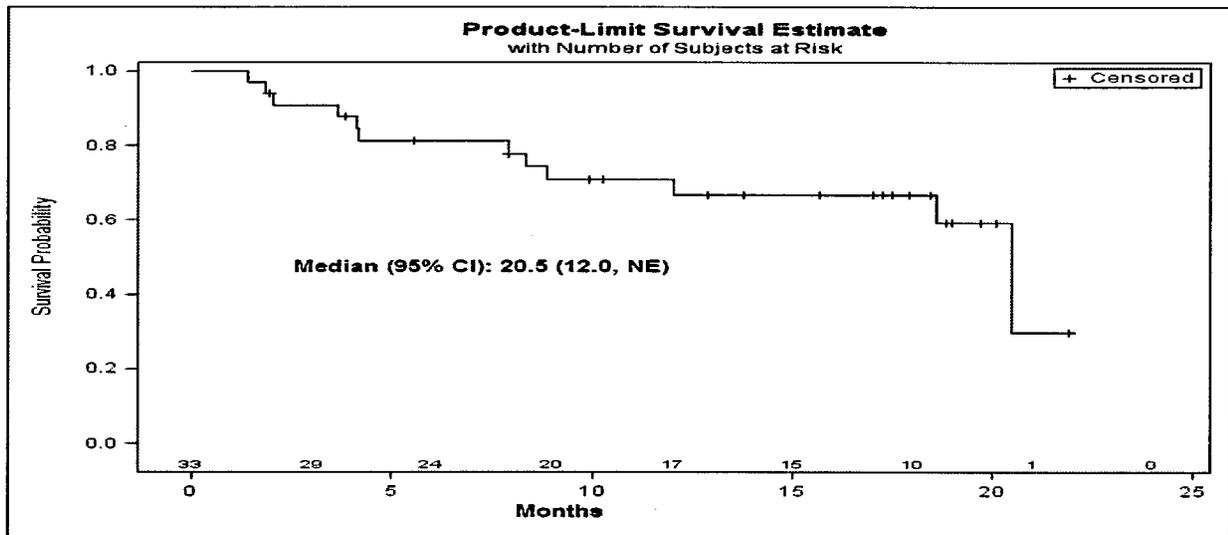
*Among 74 OR patients, 46 patients (62.1%) had progressive disease or death. The median duration of ORR was 6.7 months with 95% CI of (4.0, 14.8).*

*Among 41 PR patients, 34 patients (82.9%) had progressive disease or death. The median duration of PR was 3.5 months with 95% CI of (2.2, 4.1).*

**Figure 1 : Kaplan-Meier Plot for Duration of Objective Response Rate with Updated Datasets**



**Figure 2 : Kaplan-Meier Plot for Duration of Complete Remission with Updated Datasets**



The sensitivity analysis for ORR and duration of responses was performed using the best CT time response based on 1999 Cheson criteria with the updated datasets. There were 10 CR, 63 PR, 25 SD and 3 PD using CT time point response. Among 65 PR responses, if sum of the products of the diameters of the index lesion (SPD) percent change from baseline  $\leq 75\%$  then the PR responses was changed to CRu unless PR response had achieved earlier than the time of SPD percent change from baseline  $\leq 75\%$ . The results were 10 CR, 34 CRu, 29 PR, 25 SD and 3 PD.

The duration of response was censored at the last CT dates if patients did not have PD. For patients who had PD, the duration of response was calculated from the start dates of response (CR, CRu, or PR) to either PD dates, last CT dates, or start dates of other anticancer treatment.

If there was no last tumor assessment date, then the duration of response was one day. The sensitivity analysis results using the CT time response based on 1999 Cheson criteria are summarized in Table 18.

**Table 18: FDA’s Sensitivity Efficacy Analysis Results Using CT Time Response Based on 1999 Cheson Criteria with Updated Datasets**

	ITT Population (N=102)
Objective Response (95% CI)	73 (71.5%) (62.8, 79.2)
CR	10
CRu	34
PR	29
Duration of ORR (Months)	
Median	6.6
95% CI	(3.6, 14.8)
Complete Response (CR+CRu) (95% CI)	44 (43.1%) (34.3, 52.3)
Duration of CR+CRu (Months)	
Median	NE
95% CI	(6.3, NE)
Partial Response (PR) (95% CI)	29 (28.4%) (20.8, 37.2)
Median	3.2
95% CI	(2.0, 3.5)

The sensitivity analysis of the ORR using CT time response was 73 patients (71.5%). The duration of ORR was 6.6 months with 95% CI of (3.6, 14.8). The sensitivity ORR analysis results were robust to the primary analysis results. The sensitivity analysis for CR+CRu responses based on 1999 Cheson criteria using CT time response was 44 patients (43.1%) and the median duration of CR+CRu was not estimable. The sensitivity analysis of the partial remission was 29 patients (28.4%) and the duration of PR was 3.2 months with 95% CI of (2.0, 3.5).

The PFS and OS analyses based on updated datasets are performed as for exploratory analyses. As this is a single arm study, caution should be taken when interpreting the results of progression-free survival and overall survival analyses.

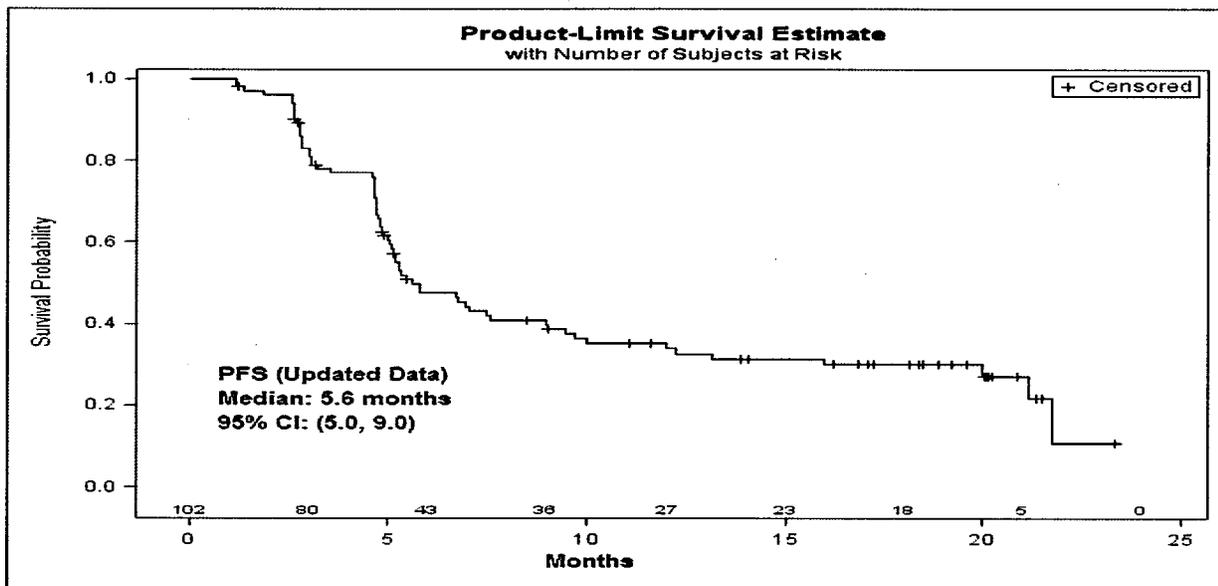
The PFS analysis results based on updated datasets are summarized in Table 19.

**Table 19: Progression-Free Survival per IRF and Investigators' Assessments with Updated Datasets**

	ITT Population (N=102)	
	IRF	Investigators' Assessment
PFS		
Number of Events	69 (67.6%)	65 (63.7%)
Duration of PFS (Months)		
Median	5.6	9.3
95% CI	(5.0, 9.0)	(7.1, 12.2)

Based on IRF, 69 patients (67.6%) had either disease progression or death among 102 ITT patients. The median PFS by IRF was 5.6 months with 95% CI of (5.0, 9.0). Based on investigators' assessments, 65 patients (63.7%) had either progression or died. The median PFS by the investigators' assessments was 9.3 months with 95% CI of (7.1, 12.2).

**Figure 3 : Kaplan-Meier Plot for Progression-Free Survival with Updated Dataset**



There were total of 5 patients who were diagnosed as having PD based on the investigators' assessments analysis, but were censored at the time of assessment based on the IRF analysis with the updated efficacy datasets. The censoring is likely informative for these 5 patients. The supportive analysis was performed by taking the first time to progression disease between the investigators' assessments and the IRF assessments. Supportive analysis results showed that 74 patients out of 102 patients (72.5%) had PD or death. The estimated median PFS time was 5.29 months with 95% CI of (4.8, 7.5).

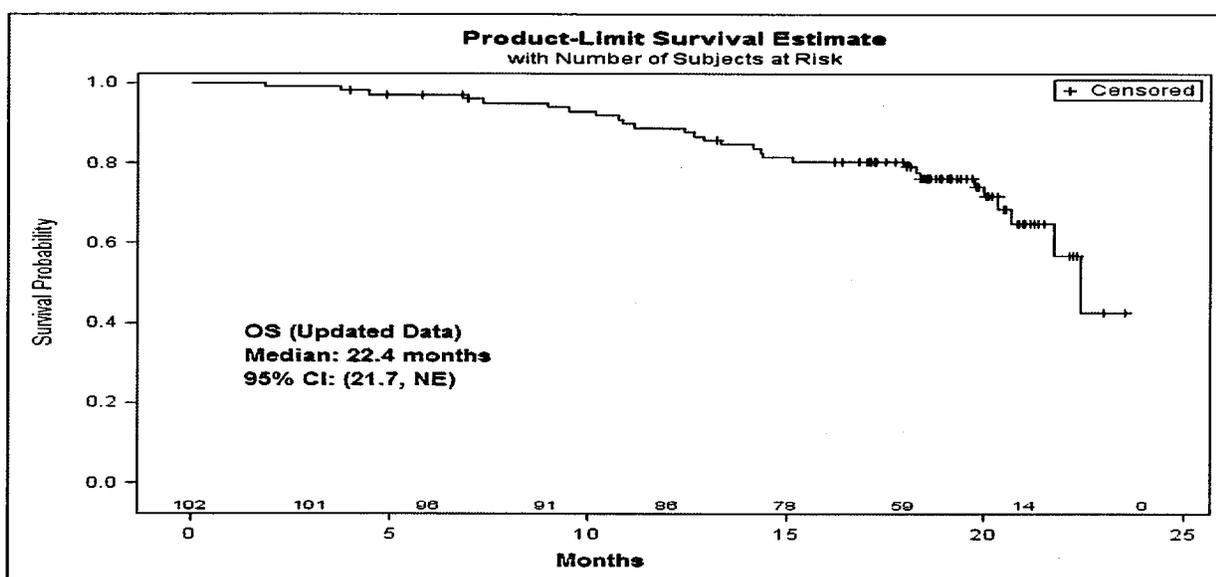
The overall survival analysis results with updated datasets are summarized in Table 20.

**Table 20: Overall Survival Results with Updated Datasets**

	ITT Population (N=102)
OS	
Number of Events	28 (27.5%)
Duration of OS (Months)	
Median	22.4
95% CI	(21.7, NE)

There were 28 deaths (27.5%) among 102 ITT patients based on March 4, 2011 data cutoff date. The median duration of OS was 22.4 months with 95% CI of (21.7, NE).

**Figure 4 : Kaplan-Meier Plot for Overall Survival with Updated Dataset**



Lost to follow-up was examined by calculating difference between the cutoff date of March 4, 2011 and the censoring dates for censored patients based on the disease progressive assessment schedule of every 12 weeks. The time between censoring date and the cutoff date for CR, ORR, PFS and OS are summarized in Table 21.

**Table 21: Time between Censoring Date and the Data Cutoff Date (March 4, 2011) for CR, ORR, PFS and OS Duration**

	≤12 weeks	13-24 weeks	25-36 weeks	>36 weeks
Duration of CR	5	5	3	8
Duration of ORR	8	9	1	10
Duration of PFS	17	2	2	8
Duration of OS	52	5	0	5

*There are 16 CR patients and 20 ORR patients who missed their most recent disease assessments, 11 with CR (censored time  $\leq 13.8$  months) and 11 with ORR (censored times  $\leq 17.2$ ) who missed their two most recent disease assessments prior to the data cutoff date.*

*There are 12 patients with PFS and 10 patients with OS who missed their most recent disease assessments, 10 with PFS and 5 with OS who missed their two most recent disease assessment prior to the data cutoff date.*

*The worst case sensitivity analyses treating patients who missed their two most recent disease assessments as events in the duration of CR and ORR were performed and the results are summarized in Table 22.*

**Table 22: Worst Case Sensitivity Analyses for Duration of Responses with Updated Datasets**

	ITT Population (N=102)
Complete Remission	33 (32.3%)
Number of Events	23 (22.5%)
Duration of CR (Months)	
Median	12.9
95% CI	(7.9, 18.9)
Objective Response	74 (74.5%)
Number of Events	57 (55.9%)
Duration of ORR (Months)	
Median	5.2
95% CI	(3.6, 8.8)
Partial Remission	41 (40.2%)
Number of Events	37 (36.3%)
Duration of PR (Months)	
Median	3.5
95% CI	(2.1, 4.1)

*In the worst case sensitivity analyses, the duration of CR was 12.9 months with 23 events among 33 CR (95%CI: 7.9, 18.9), the duration of ORR was 5.3 months with 57 events among 57 ORR (95% CI: 3.6, 8.8), and the duration of PR was 3.5 months with 37 events among 41 PR (95% CI: 2.1, 4.1).*

**Conclusion for Efficacy Endpoints:**

The applicant's primary endpoint of ORR based on IRF were 76 patients out of 102 patients (74.5%: 95% CI: 64.9, 82.6). The objective response rates results based on the investigators' assessments (71.6%) was similar.

The applicant's complete remission was 35 patients (34.3%: 95% CI: 25.2, 44.4). The complete remission based on the investigator's assessments (33.3%) was consistent.

The exact concordance rate between the investigator's assessments and the IRF assessments was 43 out of 102 patients (42.2%). There were 53 patients' agreement (52.0%) for CR and PR between IRF and the investigator's assessments among 102 ITT patients. The PET scan showed 61 patients had positive results. Two PET scan positive patients were categorized as CR in the applicant's analysis.

The FDA clinical reviewer changed 6 patients' responses (3 CR to PR; 1 PR to CR; 2 PR to SD). The FDA primary endpoint of objective response based on IRF was 74 patients out of 102 patients (72.5%: 95% CI: 63.9, 80.1). The FDA analysis had 33 patients with CR (32.4%: 95%CI: 23.3, 42.3).

The applicant's median duration of ORR was 6.7 months based on IRF (42 PD out of 76 ORR) with 95% CI of (3.7, 12.0). The applicant's median duration of ORR based on the investigators' assessment was 10.9 months (36 PD out of 73 ORR) with 95% CI of (7.1, NE). The median duration of ORR for the investigators' assessments was 3.2 months longer than that of IRF.

The applicant's median duration of CR was not reached (12 PD out of 35 CR) with 95% CI of (8.8, NE). The median duration of CR for the investigators' assessments was also not estimable (7 PD out of 34 CR).

The median duration of ORR was 6.7 months based on FDA evaluation (46 PD out of 74 ORR) with 95 % CI of (4.0, 14.8). The median duration of CR based on FDA evaluation was 20.5 months (12 PD out of 33 CR) with 95 % CI of (12.0, NE). The median duration of PR based on FDA evaluation was 3.5 months (34 PD out of 41 PR) with 95% CI of (2.2, 4.1).

The applicant's PFS analysis, 64 patients (63%) had either disease progression per IRF or died. The median PFS was 5.8 months with 95% CI of (5.0, 9.0).

The number of patients with PD was 64 (63%) based on IRF and 57 (55.9%) based on the investigators' assessments, respectively. The IRF median time to PFS was 5.8 months and the investigators' assessments median time to PFS was 9.0 months, respectively. The sensitivity analysis including 6 patients who were diagnosed as having PD based on the investigators' assessments, but were censored at the time of assessment based on the IRF assessments as PD was performed because the censoring is likely informative. The median time to the first of PD by the investigators' assessment or by the IRF assessments was 5.3 months.

The number of death was 13 out of 102 patients (12.7%) based on August 4, 2010 data cutoff date. The median duration of OS has not reached yet.

The median duration of ORR based on FDA evaluation using the updated data with cutoff date of March 4, 2011 was 6.7 months (95% CI: 4.0, 14.8) with 46 events among 74 ORR response patients. The medial duration of CR was 20.5 months (95% CI: 12.0, NE) with 12 events among

33 CR patients. The median duration of PR was 3.5 months (95% CI: 2.2, 4.1) with 34 events among 41 PR patients.

A sensitivity analysis was performed using CT time response based on 1999 Cheson criteria with the updated datasets. The sensitivity analysis results using CT time response had 73 patients (71.5%) with an OR. The median duration of OR was 6.6 months with 95% CI of (3.6, 14.8). The sensitivity ORR analysis results were robust to the primary analysis results. The sensitivity analysis based on 1999 Cheson criteria using CT time response had 44 patients (43.1%) with a CR+CRu and the median duration of CR+CRu was not estimable. The sensitivity analysis had 29 patients (28.4%) with a PR and the median duration of PR was 3.2 months with 95% CI of (2.0, 3.5).

The progression-free-survival analyses by IRF and by investigators' assessments were performed with the updated datasets. Based on IRF, 69 patients (67.6%) had either disease progression or died among 102 ITT patients. The median PFS by IRF was 5.6 months with 95% CI of (5.0, 9.0). Based on investigators' assessments, 65 patients (63.7%) had either progression or died. The median PFS by the investigators' assessments was 9.3 months with 95% CI of (7.1, 12.2).

There were total of 5 patients who were diagnosed as having PD based on the investigators' assessments analysis, but were censored at the time of assessment based on the IRF analysis in the updated efficacy data. The censoring is likely informative for these 5 patients. The supportive analysis was performed by taking the first time to progression disease between the investigators' assessments and the IRF assessments. Supportive analysis results showed that 74 patients out of 102 patients (72.5%) had PD or death. The estimated median PFS time was 5.29 months with 95% CI of (4.8, 7.5) with the updated datasets.

The overall survival analysis was performed with the updated datasets. There were 28 deaths (27.5%) among 102 ITT patients based on March 4, 2011 data cutoff date. The median duration of OS was 22.4 months with 95% CI of (21.7, NE).

Lost to follow-up was examined by calculating the difference between the cutoff date of March 4, 2011 and the censoring dates for censored patients based on the disease progressive assessment schedule of every 12 weeks. There are 16 CR patients and 20 OR patients who missed their most recent disease assessments, 11 with CR (censored time  $\leq$  17.2 months) and 11 with OR (censored times  $\leq$  13.8) of which missed their two most recent disease assessments prior to the data cutoff date.

The worst case sensitivity analyses were performed taking patients who missed their two most recent disease assessments as events in the duration of CR, ORR and PR. The duration of CR was 12.9 months with 23 events among 33 CR (95%CI: 7.9, 18.9), the duration of ORR was 5.3 months with 57 events among 74 ORR (95% CI: 3.6, 8.8), and the duration of PR was 3.5 months with 37 events among 41 PR (95% CI: 2.1, 4.1) with updated datasets.

There are 12 patients with PFS and 10 patients with OS who missed their most recent disease assessments, 10 with PFS and 5 with OS of which missed their two most recent disease assessment prior to the data cutoff date.

### 3.3 Evaluation of Safety

For a detailed summary of the evaluation of safety refer to the review by Dr. Angelo De Claro.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

These subgroup analyses should be considered with caution.

### 4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses for gender, race and age groups (<65 years versus ≤ 65 years) of the primary endpoint of ORR and the secondary endpoints of CR are summarized in Table 23.

**Table 23: Subgroup Analyses of FDA Complete and Objective Responses: Age, Gender, Race and Country.**

	N	CR		ORR	
		n (%)	95% CI	n (%)	95%CI
Age					
<40	77	25 (32.5)	23.4, 42.8	58 (75.3)	65.6, 83.3
≥40	25	8 (32.0)	18.0, 49.4	16 (64.0)	46.5, 78.9
Gender					
Female	54	20 (37.0)	25.9, 49.4	41 (75.9)	64.3, 85.0
Male	48	13 (27.1)	17.0, 39.6	33 (68.8)	56.0, 79.6
Race					
White	89	29 (32.6)	24.0, 42.2	65 (73.0)	63.8, 80.9
Other	13	4 (30.8)	13.9, 53.8	9 (69.2)	46.2, 86.1
Country					
US	86	31 (36.0)	27.0, 45.9	65 (75.6)	66.4, 83.2
Non-US	16	2 (12.5)	4.0, 30.2	9 (56.3)	35.5, 75.3

The primary endpoint of ORR was little higher for age <40 years old patients (75.3%) than that of age ≥40 years old patients (64.0%), but CR was similar. Female patients had little higher ORR and CR (75.9% and 37.0%) than male patients (68.8% and 27.1%). The ORR and CR were also higher in US patients (75.6% and 36.0%) compared to Non-US patients (56.3% and 12.5%). However, the number of Non-US was a small sample size with only 9 patients.

## 4.2 Other Special/Subgroup Populations

The primary endpoint of FDA ORR and secondary endpoint of FDA CR analyses were performed by disease characteristics. Subgroup analyses results by baseline characteristics are summarized in Table 24.

**Table 24: Subgroup Analyses for Objective and Complete Responses: Baseline Characteristics**

	N	CR		ORR	
		n (%)	95% CI	n (%)	95% CI
Disease Stage					
I & II	51	23 (45.1)	32.9, 57.7	42 (82.4)	71.4, 90.2
III & IV	47	9 (19.1)	10.7, 28.7	28 (59.6)	46.4, 71.7
Disease Status					
Refractory	43	13 (30.2)	19.1, 43.7	31 (72.1)	58.8, 82.8
Relapse	59	20 (33.9)	23.6, 45.6	43 (72.9)	61.6, 82.2
B Symptom					
Yes	35	10 (28.6)	16.3, 43.3	26 (74.3)	59.9, 85.4
No	67	23 (34.3)	24.5, 45.4	48 (71.6)	60.9, 80.7
Primary Refractory Disease	72	25 (34.7)	25.1, 45.4	50 (69.4)	59.0, 78.6
ASCT to Relapse Post-ASCT					
≤ 1 Year	72	16 (22.2)	14.4, 32.0	51 (70.8)	60.4, 79.8
> 1 Year	30	17 (56.7)	40.6, 71.6	23 (76.7)	61.4, 87.7

The ORR and CR were higher for patients with baseline disease stage I and II (82.4% and 45.1%) than that of baseline disease stage of III and IV (59.6% and 19.1%). The ORR and CR for the disease status and B symptom status were similar. The objective and complete response rates for patients with primary refractory disease were 69.4% and 34.7%, respectively. The objective response rate was little higher for patients with ASCT to relapse POST-ASCT > 1 year (76.7%) than patients with ASCT to relapse POST-ASCT ≤ 1 year (70.8%). The complete response was much higher for patients with ASCT to relapse POST-ASCT > 1 year (56.7%) than patients with ASCT to relapse POST-ASCT ≤ 1 year (22.2%).

The forest plots of subgroup analyses results for ORR and CR are in Figures 5 and 6.

Figure 5 : Forest Plot of Subgroup for FDA ORR

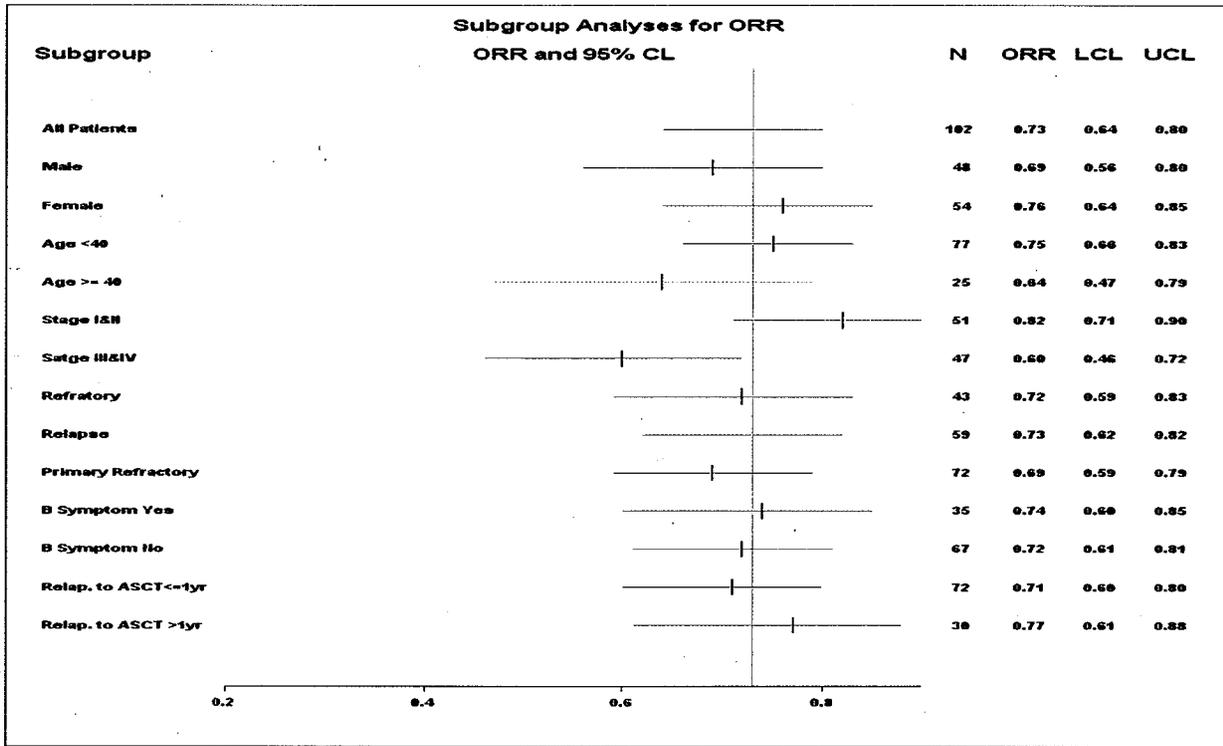
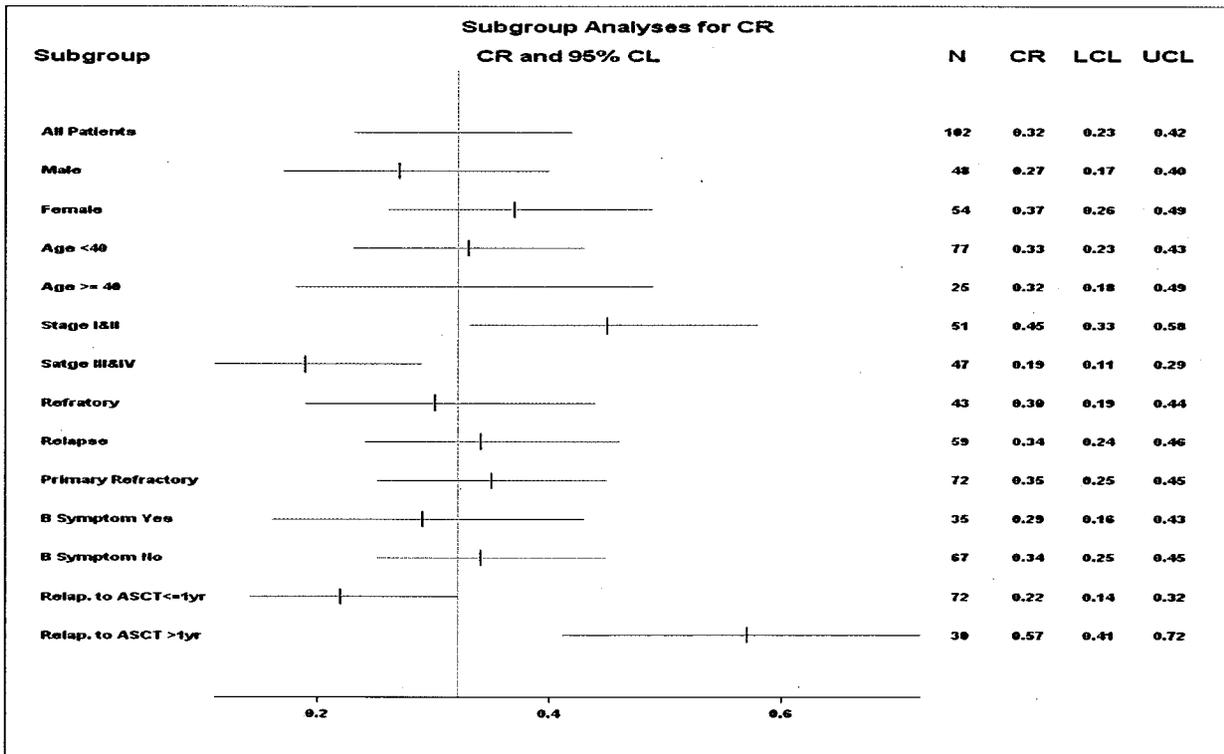


Figure 6 : Forest Plot of Subgroup Analyses for FDA CR



## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

There were no statistical issues that impact the overall conclusion in the efficacy evaluation. The summary of the findings are as follows;

- The applicant's primary endpoint of objective response based on IRF was 76 patients out of 102 patients (74.5%: 95% CI: 64.9, 82.6). The objective response rates results based on the investigators' assessments (71.6%) was consistent. The applicant's complete remission response was 35 patients (34.3%: 95% CI: 25.2, 44.4). The complete remission response based on the investigator's assessments (33.3%) was similar.
- The exact concordance rate between the investigator and IRF was 43 out of 102 patients (42.2%). There were 53 patients' agreement (52.0%) for CR and PR between the IRF assessments and the investigator's assessments among 102 ITT patients. The PET scan showed 61 patients had positive results. Two PET scan positive patients were categorized as CR in the applicant's analysis.
- The FDA changed 6 patients' responses (3 CR to PR; 1 PR to CR; 2 PR to SD) and rerun the analysis. The FDA primary endpoint of objective response based on IRF was 74 patients out of 102 patients (72.5%: 95% CI: 63.9, 80.1). The FDA complete response based on IRF was 33 patients (32.4%: 95% CI: 23.3, 42.3).
- The applicant's median duration of the objective response was 6.7 months based on IRF (42 PD out of 76 ORR) with 95% CI of (3.7, 12.0). The applicant's median duration of objective response based on the investigators' assessment was 10.9 months (36 PD out of 73 ORR) with 95% CI of (7.1, NE). The median duration of objective response for the investigators' assessments was 3.2 months longer than that of IRF. The applicant's median duration of the complete remission was not reached (12 PD out of 35 CR) with 95% CI of (8.8, NE). The median duration of the complete remission for the investigators' assessments was not also estimable (7 PD out of 34 CR).
- The FDA median duration of objective responses based on the updated data with cutoff date of March 4, 2011 was 6.7 months (95% CI: 4.0, 14.8) with 46 events among 74 ORR response patients. The median duration of complete response was 20.5 months (95% CI: 12.0, NE) with 12 events among 33 CR patients. The median duration of partial remission was 3.5 months (95% CI: 2.2, 4.1) with 34 events among 41 PR patients.
- A sensitivity analysis was performed using CT time response based on 1999 Cheson criteria with the updated dataset. The sensitivity analysis results using CT time response had 73 patients (71.5%) with an OR. The median duration of objective response was 6.6 months with 95% CI of (3.6, 14.8). The sensitivity ORR analysis results were robust to the primary analysis results. The sensitivity analysis based on 1999 Cheson criteria using CT time

response had 44 patients (43.1%) with a CR+CRu and the median duration of CR+CRu was not reached. The sensitivity analysis of partial response had 29 patients (28.4%) with a PR and median duration of PR was 3.2 months with 95% CI of (2.0, 3.5).

- There are 16 CR and 20 OR patients who missed their most recent disease assessments, 11 with CR (censored time  $\leq 17.2$  months) and 11 with OR (censored times  $\leq 13.8$ ) of which missed their two most recent disease assessments prior to the data cutoff date of March 4, 2011. All of these 11 patients had short censored durations of ORR. Treating the censoring as non-informative may inflate the estimated median duration.
- The worst case sensitivity analyses for ORR and CR were performed treating as events for those patients who missed their two most recent disease assessments. The median OR duration was 5.2 months (95% CI: 3.6, 8.8) with 57 events among 74 OR patients, the CR median duration was 12.9 months (95% CI: 7.9, 18.9) with 23 events among 33 CR patients and the PR median duration was 3.5 months with 37 events among 41 PR patients (95% CI: 2.1, 4.1).

As this is a single arm study, caution should be taken when interpreting the results of progression-free survival and overall survival analyses.

- The progression-free-survival analyses by IRF and by investigators' assessments were performed with the updated datasets. Based on IRF, 69 patients (67.6%) had either disease progression or died among 102 ITT patients. The median PFS by IRF was 5.6 months with 95% CI of (5.0, 9.0). Based on investigators' assessments, 65 patients (63.7%) had either progression or died. The median PFS by investigators' assessments was 9.3 months with 95% CI of (7.1, 12.2).
- There were total of 5 patients who were diagnosed as having PD based on the investigators' assessments analysis, but were censored at the time of assessment based on the IRF analysis in the updated efficacy data. The censoring is likely informative for these 5 patients. The supportive analysis was performed by taking the first time to progression disease between the Investigators' assessments and the IRF assessments. Supportive analysis results showed that 74 patients out of 102 patients (72.5%) had PD or death. The estimated median PFS duration was 5.29 months with 95% CI of (4.8, 7.5).
- The overall survival analysis was performed with the updated datasets. There were 28 deaths (27.5%) among 102 ITT patients based on March 4, 2011 data cutoff date. The median duration of OS was 22.4 months with 95% CI of (21.7, NE).

## 5.2 Conclusions and Recommendations

The observed objective response, complete response and duration of responses reasonably likely predict clinical benefit in patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant. There are limitations to examine the risk-benefit assessments and the long-term safety for this drug because this trial is a single arm trial.

The advisory committee meeting for oncology drug product was held on July 14, 2011 for BLA submissions, 125388/0 (SG035-0003) and 125399/0 (SG035-0004). The advisory committees voted unanimously (10-0) for accelerated approval. They are concerned about lack of long-term safety information and the limitation of risk-benefit determination. The questions and voting results of advisory committee meeting are presented in the Appendices.

## APPENDICES

Questions and voting results of advisory committee meeting are as follows.

For this application, consideration for accelerated approval would be consistent with regulatory actions taken in the past decade for similar hematology applications based on single arm clinical trials.

1. **VOTE:** The FDA has identified limitations of trial SG035-0003. Should the FDA grant accelerated, regular, or non-approval for Brentuximab vedotin for the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant?

- A. ACCELERATED APPROVAL
- B. REGULAR APPROVAL
- C. NO APPROVAL
- D. ABSTAIN

Vote results:

A.: 10

B. C. and D: 0

2. The AETHERA trial is an ongoing Phase 3, double-blind, placebo controlled, randomized trial of post-transplant therapy in patients with Hodgkin lymphoma.
  - Patients may not be in remission at the time of randomization, which raises concerns about the heterogeneity of the study population.
  - The risk-benefit assessment would be different between patients with no residual disease (i.e., CR) compared to patients with active disease.
  - The primary endpoint is progression-free survival (PFS).
  - The AETHERA trial is powered to detect a PFS hazard ratio of 0.667, corresponding to a 6 month improvement of PFS.

**DISCUSS:** Please comment on the following issues regarding the AETHERA trial.

- a. Should the inclusion criteria have been limited to patients with no active disease (i.e., CR) post transplant?

- b. What is the most appropriate primary endpoint in this trial (progression-free survival or overall survival) to demonstrate clinical benefit?

**SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Kyung Yul Lee, Ph.D.

*Kyung Yul Lee*

Date: 7/28/2011

Concurring Reviewer(s):

Statistical Team Leader: Mark Rothmann, Ph.D.

*Mark Rothmann 7/28/2011*

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

*Rajeshwari Sridhara 7/28/2011*

cc:

HFD-107/ MS. Akinsanya

HFD-107/ Dr. De Claro

HFD-107/ Dr. Virginia Kwitkowski

HFD-107/Dr. Anne Farrell

HFD-711/ Dr. Kyung Yul Lee

HFD-711/Dr. Mark Rothmann

HFD-711/Dr. Rajeshwari Sridhara

HFD-700/Ms. Lillian Patrician

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## CHECK LIST

Number of Pivotal Studies: one

### Trial Specification

Specify for each trial:

**Protocol Number (s):** 1

**Protocol Title (optional):**

**Phase:** 2

**Control:** No Control

**Blinding:** Open-Label

**Number of Centers:** 25

**Region(s) (Country):** US, France, India

**Duration:** ~18 months

**Treatment Arms:** SGN-35

**Treatment Schedule:** 1.8 mg/kg as a single outpatient intravenous (IV) infusion on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity a minimum of 8 to 16 cycles.

**Randomization:** No

**Primary Endpoint:** Objective response rates (CR+PR)

**Primary Analysis Population:** ITT

**Statistical Design:** Single arm

**Primary Statistical Methodology:** Exact 95% CI

**Interim Analysis:** No

**DSMB:** Yes

**Sample Size:** N=102

**Sample Size Determination:** Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

95% confidence (two-sided) that the true ORR is greater than 20%.

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No.
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the **Covariates** pre-specified in the protocol? No.
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? Treated as non-response in analysis of response rate; treated as ignorable for time-to event endpoints
- Was there a **Multiplicity** involved? No.

If yes,

Multiple Arms (Yes/No)?

Multiple Endpoints (Yes/No)?

Which method was used to control for type I error?

- **Multiple Secondary Endpoints:** Are they being included in the label? If yes, method to control for type 1 error. Secondary endpoints of CR and duration of responses are described the proposed label (without control of type 1 error).

**Were Subgroup Analyses Performed (Yes/No)?** Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?

No

- Overall, was the study positive (Yes/No)? Yes

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 125388

**Applicant:**

**Stamp Date:** 2/28/2011

**Drug Name:**

**NDA/BLA Type:**BLA

On initial overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			No define.pdf file

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

<u>Kyung Yul Lee</u>	<u>3/30/2011</u>
Reviewing Statistician	Date
<u>Mark Rothman</u>	<u>3/30/2011</u>
Supervisor/Team Leader	Date