

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125399Orig1s000

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 TEAM LEADER MEMO

CLINICAL STUDIES

NDA/BLA Serial Number: BLA 125399/0000

Drug Name: Adcetris™ (Brentuximab Vedotin)

Indication(s): Relapsed or refractory systemic ALCL

Applicant: Seattle Genetics, Inc.

Submitted Date: February 28, 2011

PDUFA Date: August 30, 2011

Review Priority: Priority

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Keywords: Response rate, interaction

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1. EXECUTIVE SUMMARY

The efficacy of Adcetris™ (Brentuximab Vedotin) was evaluated in study SG035-0004, a single arm, open-label study in patients with relapsed or refractory anaplastic large cell lymphoma (ALCL). Fifty-eight subjects at 22 sites were treated with at least one dose of brentuximab vedotin. Forty-three of these subjects were from the United States. The primary endpoint is objective response rate (ORR) per independent review. The determination of response was made in accordance with the Revised Response Criteria for Malignant Lymphoma [Cheson et. al. 2007 Journal of Clinical Oncology 25 (5)]. The first subject was enrolled on June 17, 2009. The data cutoff date for the primary endpoint was August 11, 2010. The duration of response had a data cutoff date of January 14, 2011.

Fifty of 58 subjects (86%) had a partial response (19 subjects) or a complete response (31 subjects). Twenty-four of the responders were known to have lost their response by the data cutoff date of January 14, 2011. The median duration of response was estimated as 12.6 months. The median duration of complete response was estimated as 13.2 months.

I agree with most of the analysis and conclusions of Dr. Kallappa Koti, the statistical reviewer. There are two topics of areas of disagreement with the statistical review of Dr. Kallappa Koti: the sizing of the study and the evaluation of the relationship between response rate and the number of prior therapies. This review will focus on these two issues.

1.1 The Sizing of the Study

From Dr. Koti's review, the sponsor states "Approximately 55 patients will be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power."

For a sample size of 55 subjects, the probability of observing at least 18 objective responses is 99.7% when the true response rate is 50%. The trial was sized to rule out a response rate of 20% or smaller when the true response rate was at least 50%. Having 18 of 55 subjects responding provides a two-sided 95% confidence interval of (0.207, 0.467) and a two-sided p-value of 0.014. The fact that an observed response of 33% is needed to rule out a true response rate of 20% or less, does not mean that the "Sponsor anticipated that the response rate to [sic; would] be in the neighborhood of 33%." The observed response in this study was 0.862 (50/58) with a corresponding 95% confidence interval of (0.746, 0.938) and a p-value of 4×10^{-27} to rule out a true response rate of 0.2 or less. The p-value in ruling out a true response rate of 0.5 or less was 8×10^{-9} .

1.2 Relationship between response rate and the number of prior therapies

Dr. Koti states in his review, "In this reviewer's opinion, the observed high rate of objective response may also be attributed to the number of prior cancer therapies." As noted in Dr. McGinn's clinical review 40 to 65 percent of patients with systemic ALCL develop recurrent

disease with 25 to 30 percent achieving a second complete remission frequently with duration of less than one year. Based on the history of outcomes for patients with relapsed or refractory ALCL, it seems unlikely that the response rate seen by Adcetris™ in study SG035-0004 is due to prior therapy or prior therapies.

Another issue is whether the response rate depends on the number of prior therapies. The small sample size (and the small number of non-responders) makes it difficult to reliably evaluate for differences in response rates across a factor. Additionally, an evaluation of the differences in response rates across the number of prior therapies was not pre-specified. Below is a reproduction of Table 5.1.1 in Dr. Koti’s review

Table 5.1.1: Overall response by the number of prior cancer therapies

# of prior cancer therapies	1	2	3	4	5	6	7	8
# of subjects	8	15	16	7	8	2	1	1
# of CR/PR	5	15	13	6	8	2	0	1

Dr. Koti in his review writes “This reviewer performed two analyses to see if the objective response was associated with the number of prior cancer therapies- Chi-square test and logistic regression. Chi-square test for independence had a p-value of 0.0426 accompanied by a SAS warning: "69% of the cells have expected counts less than 5. Chi-square may not be a valid test”.”

Comments: The Chi-square test treats the number of prior cancer therapies as unordered (nominal) categories. As the number of prior therapies is a count and thus ordered a Chi-square test is not appropriate way to correlate response rate with the number of prior therapies. Additionally, as noted in the “SAS warning” the asymptotics are not likely to hold due to the great excess of zero and small counts. Therefore, the calculated p-value may not be approximately correct.

In Dr. Koti’s review, the logistic regression model $\log(p/(1-p)) = \beta x$ is fitted where x = the number of prior therapies. The fitted probabilities were provided in Dr. Koti’s review in Table 5.1.2, which is reproduced below.

Table 5.1.2: Predicted probabilities by the number of prior cancer therapies

# of prior cancer therapies	Predicted probability of response
1	0.6383
2	0.7569
3	0.8460
4	0.9065
5	0.9448
6	0.9679
7	0.9816
8	0.9895

Comments: Fitting $\log(p/(1-p)) = \beta x$ is unusual. It is not possible to conclude that there is an association (positive or negative) between the number of prior therapies and the probability of a response. The testing of $H_0: \beta = 0$ versus $H_1: \beta > 0$ confounds the testing of a positive association between the number of prior therapies and the probability of a response with whether the overall true response rate is greater than 0.5. The null hypothesis of $\beta = 0$ is equivalent to $\log(p/(1-p)) = 0$ universally (= 0 regardless of the number of prior therapies) which is equivalent to $p = 0.5$ universally. The evaluation of the fit of the estimated model $\log(p/(1-p)) = 0.57x$ is relative to the model $\log(p/(1-p)) = 0$ universally (i.e., $p = 0.5$ universally) not the model $\log(p/(1-p)) = \log 6.25$ universally or equivalently $p = 0.862$ universally (6.25 and 0.862 are the observed overall odds and relative frequency of a response).

When the model $\log(p/(1-p)) = \alpha + \beta x$ is fit, the two-sided p-value for testing $H_0: \beta = 0$ versus $H_1: \beta \neq 0$ is 0.636, signifying that there is not strong evidence of a trend in the probability of a response across the number of prior therapies. This p-value is based on the comparison of the fit of the model $\log(p/(1-p)) = 1.4655 + 0.1218x$ with the fit of the model $\log(p/(1-p)) = \log 6.25$ (i.e., $p = 50/58$). The improvement in the fit by adding a linear term for the number of prior therapies may be due to chance. Table 1 below provides the fit for various models. The primary way for evaluating the fit of a binary outcome is through the value of the likelihood function or the value of the log-likelihood. Additionally, we compare the fit based on the sum of squared error between the observed binary outcomes of response and the fitted probability of a response.

Table 1. Comparing the fit to the response data of various models.

Model	Likelihood	Log-Likelihood	Sum of squared error
$\log(p/(1-p)) = 1.4655 + 0.1218x$	8.81×10^{-11}	-23.15	6.86
$\log(p/(1-p)) = \log 6.25$	7.84×10^{-11}	-23.27	6.90
$\log(p/(1-p)) = 0.57x$	1.79×10^{-11}	-24.74	7.08
$\log(p/(1-p)) = 0$	3.47×10^{-18}	-40.20	14.5

From Table 1, we see that the model $\log(p/(1-p)) = \log 6.25$ (i.e., $p = 50/58$ regardless of the number of prior therapies) fits the response data better than the model $\log(p/(1-p)) = 0.57x$. The model $\log(p/(1-p)) = \log 6.25$ is also a simpler model than $\log(p/(1-p)) = 0.57x$. Additionally, there is very little improvement in the fit adding a term for the number of prior therapies ($\log(p/(1-p)) = 1.4655 + 0.1218x$ versus $\log(p/(1-p)) = \log 6.25$). Also, from Table 1 it is clear that the model $\log(p/(1-p)) = 0.57x$ fits much better than the model $\log(p/(1-p)) = 0$. However, as previously stated, this is not an appropriate comparison for determining whether there is a trend in the probability of a response across the number of prior therapies.

I conclude this section with general remarks involving regression through the origin.

Regression through the origin is problematic. When each component of a pair (x, y) must be positive the estimated value for β (i.e., $\sum_{i=1}^n x_i y_i / \sum_{i=1}^n x_i^2$) must be positive even when there is a negative association between x and y . Testing of $H_0: \beta = 0$ versus $H_1: \beta \neq 0$ compares the fit of

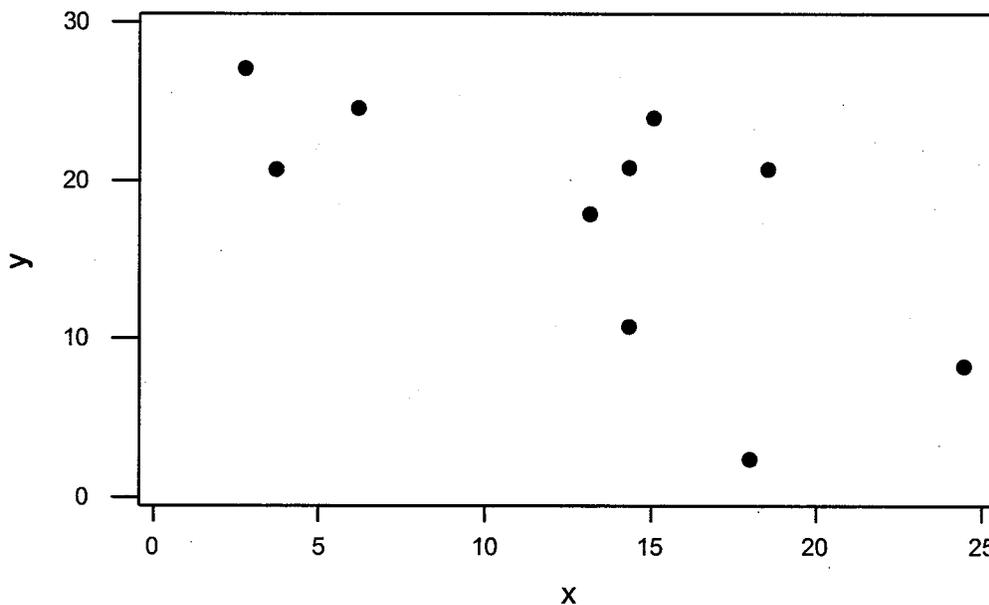
the least squares line of the form $y = \beta x$ with the fit of the line $y = 0$ (not against the fit of the line $y = \bar{y}$). Additionally, the testing of $H_0: \beta = 0$ versus $H_1: \beta > 0$ confounds the testing for a positive trend with the testing that the mean value of y is positive.

Consider the following pairs (that were generated from a model where x and y are negatively associated and $E(\hat{\beta}) \approx 1$ where $\hat{\beta}$ is the least squares estimator of β for the line $y = \beta x$) provided in Table 2 and plotted in Figure 1.

Table 1. Pairs of (x,y)

x	y
2.78	27.11
24.45	8.30
14.31	20.83
17.98	2.37
15.07	23.96
3.69	20.70
14.31	10.81
13.13	17.90
18.51	20.69
6.16	24.60

Figure 1 Plot of pairs (x,y) from Table 1



The observed Pearson's correlation is -0.664, the observed value for $\hat{\beta}$ is 0.929 with a corresponding p-value of 0.008 for testing $H_0: \beta = 0$ versus $H_1: \beta > 0$. While the line $y = 0.929x$ fits much better than the line $y = 0$, there is not a positive trend and the least squares line of the

form $y = \beta x$ fits much worse than the least squares line of the form $y = \alpha + \beta x$ (i.e., $y = 27.7 - 0.766x$) with respective sum of squared errors of 1876 and 321.

In the logistic regression example if the relative frequency of a success is greater than 0.5 for every value of x , then the estimated value for β will be positive for the model $\log(p/(1-p)) = \alpha + \beta x$, even when there is no correlation or a negative correlation between x and the probability of a success.

2. CONCLUSION AND RECOMMENDATIONS

The observed objective response, complete response and duration of responses are reasonably likely to predict or correspond to clinical benefit in patients with relapsed or refractory ALCL. Due to results solely from single-arm studies, a risk-benefit assessment and the evaluation of long-term safety are limited. An advisory committee meeting was held on July 14, 2011 for this application. The advisory committee voted unanimously (10-0) for accelerated approval.

/s/

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08/05/2011

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08/05/2011



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Biometrics Division: DB V / CDER
Statistical Reviewer: Dr. Kallappa M. Koti
Concurring Reviewers: Dr. Mark Rothmann, Lead Mathematical Statistician
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Medical Division: DHP
Clinical Team: Dr. Karen McGinn
Dr. Virginia Kwitkowski, Team Leader
Project Manager: Ms. Lara Akinsanya

Keywords: Response rate, confidence interval, p-value, Kaplan-Meier analysis.

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1. EXECUTIVE SUMMARY

This is Seattle Genetics submission biologic license application (BLA) No. 125399 for Adcetris™ (Brentuximab Vedotin) for the treatment of relapsed or refractory systemic anaplastic large cell lymphoma (ALCL). The Sponsor is seeking regular approval for Adcetris™. The Sponsor's efficacy claim is based on one phase 2 study in patients with relapsed or refractory ALCL (SG035-0004). The phase 2 study was a single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of Brentuximab Vedotin as a single agent in patients with relapsed or refractory ALCL. Efficacy claim is based on the objective response rate (ORR) per independent review facility (IRF). The data cutoff dates were 11 August 2010 for the original data and 14 January 2011 for the updated durability data.

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 to 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 from study SG035-0004 that impact them with regards to the demonstration of efficacy are summarized as follows.

- Objective response rate per IRF was 86% [95% CI: (77%, 95%)]. This observed response rate was significantly higher than 20% (p-value < 0.0001).
- Complete response rate per IRF was 57% [95% CI: (44%, 70%)].
- In this reviewer's opinion, this high response rate may not be attributed to Adcetris™ treatment alone; it may be attributed to the number of prior cancer therapies as well.
- Median time to objective response was 6 weeks. Median time to CR was 14 weeks.
- No definitive conclusion could be made regarding the durability of the objective response.
- No definitive conclusion could be made regarding the durability of the complete response.
- In this reviewer's opinion, the sample size for the clinical trial SG035-0004 was underestimated.

2. INTRODUCTION

2.1 Overview

The Sponsor has used three clinical studies to support efficacy of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL): one phase 2 study

in patients with relapsed or refractory ALCL (SG035-0004) and two phase 1 studies in patients with relapsed or refractory CD30-positive malignancies (SG035-0001 and SG035-0002). The phase 1 studies were dose-escalation studies. This review does not discuss the phase 1 studies.

The phase 2 study was a single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of Brentuximab Vedotin as a single agent in patients with relapsed or refractory ALCL. Eligible patients had relapsed or refractory systemic ALCL, had received front-line chemotherapy with curative intent, and had histologically-documented CD30-positive disease. The seventy-eight subjects were recruited in 22 sites in Belgium (1), Canada (3), France (8), Germany (3), and the United States (43). Forty-three (74%) of the subjects were from the United States of America. Fifty-eight patients received at least 1 dose of brentuximab vedotin.

The primary endpoint of the study was objective response rate (ORR) per independent review facility (IRF), a direct measure of antitumor activity. Clinical response assessments were made in accordance with the Revised Response Criteria for Malignant Lymphoma [Cheson et al. 2007; Journal of Clinical Oncology 25 (5)], which includes radiographic disease assessment by CT and/or PET scans and oncology review of clinical data. This study enrolled 58 patients at 21 study centers. The average age of subjects was 48 years. There were more males (57%) than females. Eighty-three per cent (83%) of patients were White. Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous SCT. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy two percent (72%) were anaplastic lymphoma kinase (ALK)-negative. All 58 patients received at least 1 dose of brentuximab vedotin 1.8 mg/kg administered via outpatient intravenous (IV) infusion- every 3 weeks. Patients could remain on treatment for 8-16 cycles. Brentuximab vedotin was administered on Day 1 of each 21-day cycle. Duration of treatment varied from 3 to 51 weeks. Median duration of treatment was 20 weeks. The first patient was enrolled on 17-June-2009. The date of last patient last visit for interim report was 11-April-2010. The data cutoff dates were 11 August 2010 for the original data and 14 January 2011 for the updated durability data.

2.2 Data Sources

The data format was SDTM and ADaM datasets were provided.

EDR Location: \\cber-fs3\m\CTD_Submissions\STN125388\0000 and
\\cber-fs3\m\CTD_Submissions\STN125399\00009

Datasets ADEFF.xpt, and ADTRS04.xpt, and ADSL.xpt were used in preparing this review.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data sources included Applicant study reports, data sets analyzed, and literature referenced. 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. This reviewer did not need to merge too many datasets to generate variables.

3.2 Evaluation of Efficacy

Study Design and Endpoints

The primary endpoint of the study was objective response rate (ORR) per independent review facility (IRF) assessment of best clinical response. Response assessments were made in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007, Journal of Oncology 25) per IRF. Treatment response was assessed by spiral CT of chest, neck, abdomen, and pelvis; PET scans; and clinical data. Objective response assessments were made at pre-specified time-points during the study. As shown in Table 3.2.1 and Table 3.2.2 below, response assessments were to be performed at Cycles 2, 4, 7, 10, 13, and 16 with PET at Cycles 4 and 7 only. Duration of treatment varied from 3 to 51 weeks. Median duration of treatment was 20 weeks.

Overall 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. Enrolled patients who are later determined to have the incorrect histological cancer type upon central review will be scored as non-responders for calculating the ORR.

Time to objective response, duration of objective response, progression-free survival and overall survival were key secondary endpoints.

Time to objective response was the earliest time that an objective response could formally be registered was at the first post-baseline CT restage assessment between Weeks 5 and 6.

Duration of response is defined as the time from start of the first documentation of ORR to the first documentation of objective tumor progression or to death due to any cause, whichever comes first. Duration of response was censored on the day following the date of the last radiological assessment of measured lesions documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment or stem cell transplant, or are removed from study prior to documentation of objective tumor progression. Duration of response was calculated for the subgroup of patients with ORR.

Progression-free survival (PFS) 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 comes first. PFS data was censored on the day following the date of the last radiological assessment of measured lesions documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor other than the study treatment or stem cell transplant, or are removed from study prior to documentation of objective tumor progression. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day.

Overall survival (OS) was defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive. Patients lacking data beyond the day of first dose had their survival time censored at 1 day.

Table 3.2.1: Schedule of assessments in ALCL study SG035-004

Day (D)	Screening /Baseline		Enrollment	Each 21-day Cycle			Additional Assessments	EOT	LTF*
			Within 24 hrs of first dose	D1	D2	D15	D15-21 of Cycle	30±7 Days ⁺	
Study day				1	2	15			
Visit Window	-28 to D1	-7 to D1							
Inclusion/exclusion criteria	X								
Informed consent	X		Faxed confirmation prior to study start						
Tumor specimen CD30 expression	X								
Medical history + prior disease therapies	X								
ECOG performance status		X							
SGN-35 administration				X					
Dedicated CT of chest, neck, abdomen, pelvis	X						X	X	X
PET	X						X	X	
B symptom assessment	X			X				X	
Bone marrow aspirate and biopsy	X						X		
Disease progression status + Post study treatment									X

⁺ q 12 Wks ± 1 Wk; * Days of post test dose

Table 3.2.2: IRF Assessments in ALCL study SG035-004

IRF Response Types	Baseline	Cycle 2 Restage	Cycle 4, Cycle 7 Restage	Cycle 10, Cycle 13, Cycle 16 Restage	EOT Restage	Follow-up (q 12 weeks)
CT only	X	X	X	X	X	X
CT+ Oncology Clinical Data Review	X	X	X	X	X	
CT+PET only	X		X			
CT+PET + Oncology Clinical data review	X		X			

Patient Disposition, Demographic and Baseline Characteristics

There were 25 females and 33 males. Fifty subjects (86%) had at least 2 prior cancer therapies. Fifteen subjects had an autologous stem cell transplant (ASCT) and the remaining 43 subjects had no prior ASCT.

A total of 78 patients were screened for this study, of these 58 patients received at least 1 dose of brentuximab vedotin. Twenty patients who were screened but not subsequently enrolled in the study because they did not meet at least 1 of the eligibility criteria. Eighteen patients (31%) were continuing on study treatment at the time of data lock for this report. Forty patients (69%) discontinued treatment in the study. Reasons for discontinuing treatment are provided in Table 3.2.3 below.

Table 3.2.3: Disposition of patients

Disposition: End of Treatment	Number of Patients (%)
ADVERSE EVENT	11 (27.5%)
COMPLETED	1 (2.5%)
PHYSICIAN DECISION	13 (32.5%)
PROGRESSIVE DISEASE	12 (30%)
WITHDRAWAL BY SUBJECT	3 (7.5%)
Total	40

Statistical Methodologies

Sample size determination: “Approximately 55 patients will be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power.”

Results and Conclusions

Sponsor’s results as of data cut-off date 11 August 2010:

- In the ITT analysis set of 58 patients, ORR per IRF assessment was 86% [95% CI (74.6, 93.9)]: 53% CR (31 patients) and 33% PR (19 patients). The remaining patients had SD (2 patients), PD (3 patients), were histological ineligible (2 patients), or were not evaluable for response (1 patient).

- Median time to objective response by IRF assessment was 5.9 weeks, and the median time to CR was longer, 11.7 weeks.
- Median duration of objective response per IRF assessment by Kaplan-Meier analysis has not been reached at the time of the data cut-off; the lower bound of the 95% CI was 36 weeks (range 0.3+, 45.3+).
- Among patients who achieved a best response CR, the estimated median duration of response per IRF by Kaplan-Meier analysis has not been reached.
- Median PFS per IRF assessments by Kaplan-Meier analysis has not been reached at the time of the data cut-off; the lower bound of the 95% CI was 20.1 weeks (range 3.4, 51.3+).
- At the time of database lock, 12 patients died. Median overall survival has not been reached.
- The B symptom resolution rate was 82% (14 of 17 patients with B symptoms at baseline). Median time to resolution was 3.14 weeks (range, 0.3 to 9.1).

Reviewer's results as of data cut-off date 14 January 2011

Table 3.2.4 below shows the numbers of responders (%) as assessed by IRF and investigator. Objective response (CR or PR) rate per IRF is 86% [95% CI: (77%, 95%)] whereas it is 81% [95% CI: (71%, 91%)] according to the investigator assessment. In either case, the null hypothesis that the objective response rate is less than or equal to 20% is rejected (p-value <0.0001).

Table 3.2.4: Best response in ALCL study SG035-004

Best Response	# of subjects per IRF (%)	# of subjects per INV (%)
Complete response	31 (53.4%)	34 (58.62%)
Partial response	19 (32.8%)	13 (22.41%)
Histological ineligible	2 (3.6%)	2 (3.45%)
Progressive disease	3 (5.2%)	2 (3.45%)
Stable disease	2 (3.6%)	5 (8.62%)
Missing	1 (1.8%)	2 (3.45%)
Total	58	58

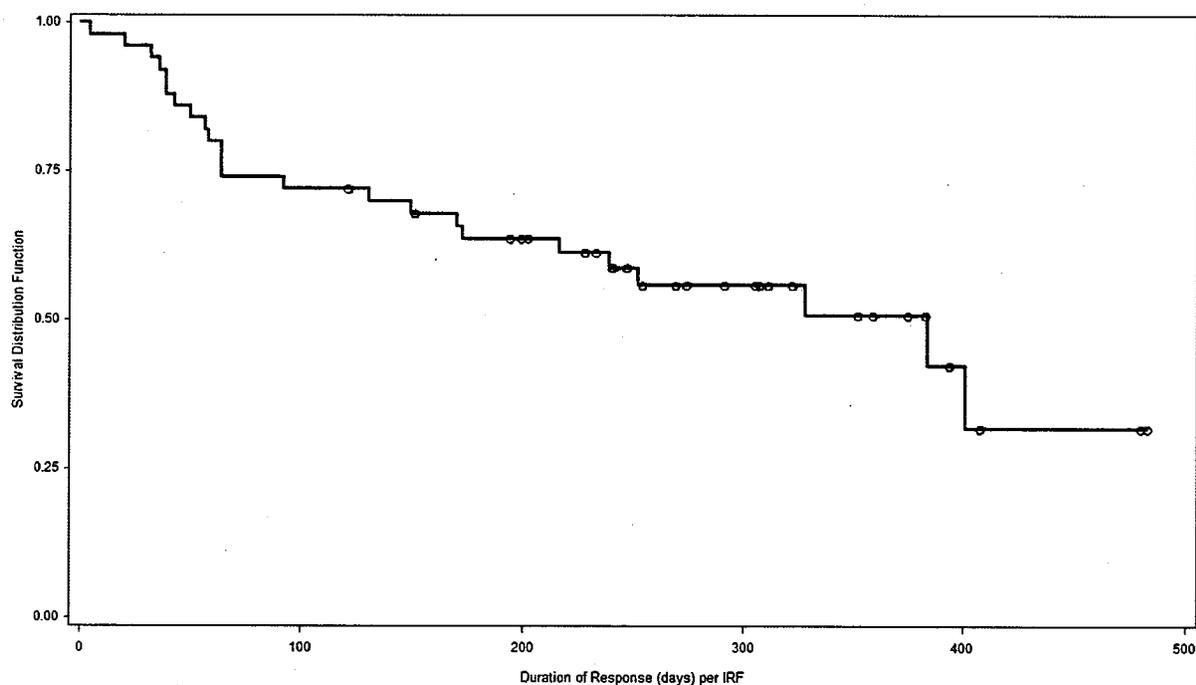
As per the updated dataset (of cutoff date: 14 January 2011), per IRF assessment, there were 33 (57%) CRs and 17 PRs. A 95% confidence on CR rate was (0.442, 0.696). Objective response rate was unchanged.

Median time to objective response was 6 weeks [CI: (5.7, 6.1)] and the median time to CR was 14 weeks [CI: (12, 20.9)].

Of the 50 responders, 24 lost response by the data cut-off date 14 January 2011. Median objective response duration was 384 days (54.8 weeks). Upper Confidence Limit is not available. There appears to be a great deal of variability in the estimated median of response duration. Kaplan-Meier survivor curve for duration of objective response is shown in Figure 3.2.1 below.

Of the 33 subjects who had a CR, 10 lost response by the data cut-off date 14 January 2011. Median complete response duration was 401 days (57.3 weeks). Upper Confidence Limit is not available.

Figure 3.2.1: Kaplan-Meier curve for duration of objective response



There was insufficient follow-up for PFS. As per IRF, there were 29 PFS events. Estimated median PFS was 406 days (1.1 years). Upper limit of a 95% confidence limit was not available. In a single arm study PFS is not interpretable.

Eighteen subjects died during the study. There was insufficient follow-up for overall survival. In a single arm study OS is not interpretable.

The mean and median of the sum of the product of diameters (SPD) of dominant nodes at baseline as per IRF were 25.11 and 15.9 cm², respectively. The range of SPD was 1.44 to 110.02 cm². The median maximum percent reduction from baseline in SPD per IRF was -83% (range, -100% to 48%) for patients who had post baseline assessment.

3.3 Evaluation of Safety

See the medical officer's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The data cut-off date for sections 4.1 and 4.2 was 14 January 2011.

4.1 Gender, Race, Age, and Geographic Region

Of the 33 male subjects, 26 (79%) achieved objective response per IRF. Of the 25 female subjects, 24 (96%) achieved objective response per IRF. Sixteen (64%) of the 25 female patients achieved complete response. Seventeen (51.5%) of the 33 male patients achieved complete response. Eight (32%) female patients achieved partial response whereas 9 (27.3%) male patients achieved partial response. Of the remaining 7 male subjects, 2 had stable disease, 3 had disease progression and 2 were histological ineligible.

Clinical study SG035-004 included only 9 subjects who were 65 years or over. Subgroup analysis by < 65 years versus ≥ 65 years is not performed. Median age was 52 years. This reviewer performed a subgroup analysis by < 52 years versus ≥ 52 years. Of the 29 younger subjects (<52 years of age), 25 (86%) achieved objective response per IRF. Of the 29 older subjects (≥ 52 years of age), 25 (86%) achieved objective response per IRF.

Out of 43 U.S. subjects, 40 (93%) achieved either CR or PR. Twenty-two (51%) subjects had complete response.

4.2 Other Special/Subgroup Populations

- Objective response and prior ASCT status were not associated. Of the 15 subjects who had an ASCT, 13 (87%) patients achieved objective response whereas 37 (86%) subjects of the remaining 43 achieved objective response.
- Of the 16 subjects who were ALK-status positive, 13 (81%) achieved objective response per IRF. Of the 42 subjects who were ALK-status negative, 37 (88%) achieved objective response per IRF.
- Of the 29 subjects who were refractory, 22 (76%) achieved objective response per IRF. Of the 29 subjects who were relapsed, 28 (96%) achieved objective response per IRF.
- Of the 17 subjects who had baseline B-symptoms, 15 (88%) achieved objective response per IRF. Of the remaining 41 subjects who did not have baseline B-symptoms, 35 (85%) achieved objective response per IRF.

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In this reviewer's opinion, the sponsor's description of sample size determination is confusing, and possibly deceptive. The Sponsor states: "Approximately 55 patients will be enrolled in this study. With a sample size of 55, observing 18 (33%) objective responses (CR or PR) would allow us to state with 95% confidence (two-sided) that the true ORR is greater than 20%. Assuming the true ORR is 50%, the study would have over 95% power." If the objective is to have an interval estimate of a parameter, sample size determination should depend on a pre-specified width of the confidence interval. The Sponsor did not follow this approach. The Sponsor based sample size determination on testing hypothesis. The Sponsor sets the rate of responders under the null hypothesis as 20% and finds sample size when the response rate is 50% under the alternative hypothesis. The Sponsor anticipated that the response rate to be in the neighborhood of 33% but set the response rate as 50% under the alternative hypothesis- just to make the sample size smaller. The required sample size for testing the above null hypothesis at $\alpha = 0.05$ (2-sided) with a power of 90% for an alternative hypothesis of 35% is 90-92.

In this reviewer's opinion, the observed high rate of objective response may also be attributed to the number of prior cancer therapies. The Table 5.1.1 below provides the numbers of subjects and the numbers of CR/PR by the numbers of prior cancer therapies.

Table 5.1.1: Overall response by the number of prior cancer therapies

# of prior cancer therapies	1	2	3	4	5	6	7	8
# of subjects	8	15	16	7	8	2	1	1
# of CR/PR	5	15	13	6	8	2	0	1

This reviewer performed two analyses to see if the objective response was associated with the number of prior cancer therapies- Chi-square test and logistic regression.

Chi-square test for independence had a p-value of 0.0426 accompanied by a SAS warning: “69% of the cells have expected counts less than 5. Chi-square may not be a valid test”.

A logistic regression model indicated that probability of response is likely to be dependent on the number of prior cancer therapies. As seen from Table 5.1.1, the minimum and maximum number of prior cancer therapies was 1 and 8, respectively. Estimated model was $\text{logit}(\hat{p}) = 0.57 \times \#$ of prior therapies. Observed regression coefficient was significantly greater than 0. The *c* statistic was equal to 0.67. The predicted probabilities of response are listed in Table 5.1.2 below.

Table 5.1.2: Predicted probabilities by the number of prior cancer therapies

# of prior cancer therapies	Predicted probability of response
1	0.6383
2	0.7569
3	0.8460
4	0.9065
5	0.9448
6	0.9679
7	0.9816
8	0.9895

Of the 50 responders, 24 lost response by the revised data (of cut-off date 14 January 2011). Median response duration was 384 days (54.8 weeks). Upper Confidence Limit is not available. In this reviewer’s opinion, duration of response can not be assessed accurately.

5.2 Conclusions and Recommendations

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 to 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 from study SG035-0004 that impact them with regards to the demonstration of efficacy are summarized as follows.

- Objective response rate per IRF was 86% [95% CI: (77%, 95%)]. This observed response rate was significantly higher than 20% (p-value < 0.0001).
- Complete response rate per IRF was 53% [95% CI: (41%, 66%)].
- In this reviewer's opinion, this high response rate may not be attributed to Adcetris™ treatment alone; it may be attributed to the number of prior cancer therapies as well.
- Median time to objective response was 6 weeks. Median time to CR was 14 weeks.
- No definitive conclusion could be made regarding the durability of the response.
- In this reviewer's opinion, the sample size for the clinical trial SG035-0004 was underestimated.

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 SG035-0004. 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?

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CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): SG035-0004

Protocol Title (optional): A Phase 2, single-arm, open-label, multicenter trial to evaluate the efficacy and safety of Brentuximab Vedotin (Adcetris™) as a single agent in patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)

Phase: 2

Control: None

Blinding: Open-Label

Number of Centers: 22

Region(s) (Country): US, Canada, Belgium, France, United Kingdom

Duration: 15 months

Treatment Arms: Brentuximab Vedotin

Treatment Schedule: 1.8 mg/kg IV every 3 weeks

Randomization: No

Ratio: NA

Method of Randomization: NA

If stratified, then the Stratification Factors: NA

Primary Endpoint: Objective response rate (ORR)

Primary Analysis Population: ITT

Statistical Design: NA

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data? NA

Margin = NA

%Retained = NA

Adaptive Design: No

Primary Statistical Methodology: Hypothesis testing, confidence intervals

Interim Analysis: No

If yes:

No. of Times:

Method:

α Adjustment: NA

α Spending Function:

DSMB: NA

Sample Size: 58

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

Statistic = z-test

Power = 95%

Δ = Not sure

α = 0.05

- 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**? No
- How were the **Missing Data** handled? NA
- Was there a **Multiplicity** involved? No
 - If yes,
 - Multiple Arms? NA
 - Multiple Endpoints? NA
 - Which method was used to control for type I error? NA
- **Multiple Secondary Endpoints:** Are they being included in the label? Yes
 - If yes, method to control for type 1 error. NA

Were Subgroup Analyses Performed? Yes

- Were there any **Discrepancies** between the protocol / statistical analysis plan vs. the study report? No
- Overall, was the study positive? Yes

/s/

KALLAPPA M KOTI

07/29/2011

MARK D ROTHMANN

07/29/2011

RAJESHWARI SRIDHARA

07/29/2011

I do not concur with reviewer's conclusion that the response rate is attributable to number of prior lines of therapy. Scientifically this is incorrect. Response is attributable to the current treatment only, when the patient's disease has relapsed or refractory to prior therapy. Secondly the sample size underestimation is not of consequence when the observed response rate is 86%. This application was discussed at ODAC on 7/14/2011. The committee members voted unanimously to grant accelerated approval. The response rate observed in this trial is reasonably likely to predict clinical benefit.

STATISTICS FILING CHECKLIST FOR BLA 125388: ALCL

NDA Number: STN 125399

Applicant: Seattle Genetics, Inc. **Stamp Date:** 2-28-2011

Drug Name: Brentuximab Vedotin

NDA Type: BLA

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

	Content Parameter	Yes	No	NA	Comments
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			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? **YES**

If the NDA/BLA is not file-able 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
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 BLA 125388: ALCL

<u>Kallappa Koti</u> Reviewing Statistician	<u>3-24-2011</u> Date
<u>Mark Rothman</u> Supervisor/Team Leader	<u>3-24-2011</u> Date