Author's response to reviews

Title: Comparison of darbepoetin alfa dosed weekly (QW) vs. extended dosing schedule (EDS) in the treatment of anemia in patients receiving multi-cycle chemotherapy in a randomized, phase 2, open-label trial

Authors:

Lee Schwartzberg (lschwartzberg@westclinic.com)
Ronald Burkes (rburkes@mtsinai.on.ca)
Barry Mirtsching (bmirtsching@cortpa.com)
Timothy Rearden (reardentp@aol.com)
Peter Silberstein (PeterSilberstein@creighton.edu)
Lorrin Yee (nwmsresearch@nwmedicalspecialties.com)
Amy Inamoto (ainamoto@amgen.com)
Tom Lillie (tlillie@amgen.com)

Version: 3 Date: 17 August 2010

Author's response to reviews:

August 16, 2010

Dr. Elizabeth Moylan
Scientific Editor, BioMed Central Cancer
Re: Manuscript #1720478622994568

Dear Dr. Moylan,

Thank you for the opportunity to revise our manuscript in response to the reviewers’ comments. Attached is a revised draft of the manuscript with the changes tracked. The figures are both embedded in the manuscript (so track changes can be visualized) and also submitted as separate EPS files. Please see our specific responses to the reviewers’ comments below.

Major Compulsory Revisions:

1. It appears that the p-values presented are for a superiority test, that is, testing the null hypothesis that there is no difference between groups. However, this study was designed as a non-inferiority study and as such the null hypothesis is that the EDS group is inferior to the QW group. The investigators should include p-values that test the null hypothesis of inferiority.

We agree that presenting p-values from a superiority test is inappropriate when the primary objective is to demonstrate noninferiority; we have removed the method for calculating p-values from the methods section and all such p-values from the paper. In addition, because concluding noninferiority based on the upper limit of a 2-sided 95% confidence interval being <0.75 g/dL (the criterion
prespecified in the protocol) is equivalent to concluding noninferiority based on a p-value being <0.05 from a 2-sided test of the null hypothesis that EDS is inferior to QW by >0.75 g/dL, we decided not to present any p-values since the confidence intervals sufficiently summarize the results.

2. The analyses for achieving hemoglobin > 11 and hematopoietic response are conducted appropriately using time to event methods. However, the investigators must give the time frame of their Kaplan-Meier estimates (13 months? 25 months?). The investigators should remove the crude percentages since they do not account for loss to followup. It should be clarified what subgroup was included in a particular analysis and why. For example, why are only 190 QW and 178 EDS patients included in the analysis of hematopoietic response?

We presented the time frame of the Kaplan-Meier (KM) estimates for these two endpoints in the summary table either by noting Week 13 or end of treatment (which was the Week 25 KM estimate since that was the maximum time allowed on-study per the protocol). We have also provided this clarification throughout the document. In addition, we have removed the crude percentages where previously presented. And finally, Table 2 (now Table 3 in the revised paper) now contains footnotes for any analysis in which the number of patients analyzed is less than the number of patients in the primary analysis set (ie, those randomized and dosed). For hematopoietic response, we had mistakenly presented the number of patients who responded as the number of patients used in the analysis; this has now been corrected and the table now shows that all patients in the primary analysis set were included in the analysis of hematopoietic response.

Minor Essential Revisions:

3. The method of analysis for the primary endpoint (linear regression with the change score as the dependent variable and randomization strata as covariates) should be included in the statistical analysis section.

In the revised paper, we have added the analysis method of the primary endpoint to the statistical analysis section of the methods.

4. The results currently shown in graphical format in figure 3 would be better presented in table format with the following columns: mean change for QW group, mean change for EDS group, mean difference between groups, confidence interval for difference between groups (which may be a one-sided confidence interval, by study design), and p-value; the shaded area in the figure 3 has no statistical meaning since the outcome is a continuous variable. Similar comment applies to the results shown in figure 5 – these results would be easier to interpret in table format.

The results presented in Figure 3 have now been reformatted into a table (Table 2 in the revised paper). No p-value is included based on our response to Comment 1. The results presented in Figure 5 have now been added to Table 3 in the revised paper.
5. The investigators state that the p-values in table 2 were obtained using the stratified chi-square test. Please clarify whether this was the log rank test.

The p-values in Table 2 (now Table 3 in the revised paper) were from a chi-square test of difference between groups in the KM proportions, which was estimated by the weighted average of the stratum differences in the proportions, with weights equal to the inverse of the variance of the stratum difference (the variance in each stratum was estimated using Greenwood’s formula). The chi-square test is described by Cochran (see reference below). However, we have now removed these p-values since, as the reviewer points out in comment 1, superiority p-values are not appropriate given the study’s objectives.


6. When reporting the mean values for the primary endpoint, the authors should use an additional significant figure, e.g. mean difference 0.14 instead of 0.1.

We have now used an additional significant figure when presenting the results of the primary endpoint in the text and in Table 2.

7. On page 9, first paragraph, the investigators state “If the upper limit of the 95% CL for the difference in mean change…is not more than 0.75 g/dL, then the conclusion from this study would be that EDS is non-inferior to QW and that the efficacy of EDS is greater than placebo.” The latter conclusion – that the efficacy of EDS is greater than placebo – is not appropriate and should be omitted.

We have omitted “…and that the efficacy of EDS is greater than placebo.” from the statement above.

Discretionary Revisions:

8. It is encouraged for the authors to follow the CONSORT statement for reporting of randomized controlled trials. For example, there is no mention of whether the study was blinded; presumably it was not blinded due to the study design, but this should be mentioned.

A clear description of the study is now included in the methods (including a statement that this was an open-label trial), and the CONSORT checklist has been reviewed to confirm that there are no more missing items in the manuscript.

In addition to the changes made in response to the reviewer’s comments above, we noted minor grammatical errors and inconsistencies in the text. These have been corrected and instances where the language has been substantially revised have been tracked. Additionally, the table of FACT-F data (Table 4) has been formatted to be consistent with the other tables. Finally, in the Results section, additional resource utilization data were included to further clarify these results by dosing schedule (QW, Q2W, and Q3W).

We would like to thank the reviewers for their thoughtful and critical review of the
manuscript. With these revisions, we hope that the manuscript is now suitable for publication in BioMed Central Cancer.

Sincerely,

Lee S. Schwartzberg, MD, FACP
West Clinic
Memphis, TN
Tel: 901-683-0055
Email: lschwartzberg@westclinic.com