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

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Author's response to reviews: see over
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Melissa Norton, MD
Editor-in-Chief, BMC Cancer

RE: 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

Dear Dr. Norton:

On behalf of the other authors, I wish to express our appreciation for the thorough review provided by the referees and have revised the above manuscript accordingly.

A point-by-point detailed response is provided below. In general, many comments concerned statistical methods and analyses. Accordingly, the Methods portion of the manuscript is the most altered. After carefully reviewing the manuscript, we also made a few minor edits for clarity and removed a few redundant references.

We believe the amended manuscript is much improved. Given the widespread occurrence of patients with anemia due to chemotherapy in oncology practices, we believe that the readership of BMC Cancer will be greatly interested in this study. We thank you for your consideration of the revised manuscript.

Please contact me directly if any questions should arise.

Sincerely yours,

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Major Compulsory Changes

Eric Winquist 1: The question posed by the authors is clearly stated: to evaluate the noninferiority of darbopoetin alfa given in an extended dosing schedule (EDS) compared to a weekly dosing schedule (QW) in patients with chemotherapy induced anemia. However, this is a phase 3 question and the trial is titled a “phase 2” trial. The tone of the authors conclusions are pragmatic ones and most consistent with a phase 3 trial and the sample size is much larger than would be expected for a phase 2 trial. So this reviewer assumed that “phase 2” in the title is a typographical error. If this is a phase 2 trial, then the authors should explain how this is the case in terms of the objectives of the trial.

Response: We acknowledge that though we designated this trial as phase 2 (not a typo), the size and the practical nature of the study questions are indicative of a phase 3 trial. However, other aspects of this study are more in keeping with a phase 2 trial. These include the nature of the comparison (e.g., open-label, no placebo or other comparator molecule) and that comparing the optimal dosing schedules (typically a phase 2 objective) was key to the trial. Also of importance in determining trial phase (per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E8 guidelines) was whether this was a therapeutic exploratory trial (typically phase 2) vs. a therapeutic confirmatory trial (typically phase 3). While there have been studies comparing Q3W darbepoetin alfa to QW epoetin alfa or QW darbepoetin alfa, there has not yet been a major publication of trial data concerning QW darbepoetin alfa vs. an extended dosing schedule (EDS) in which patients received either Q2W or Q3W darbepoetin alfa. Therefore due to these various considerations, this trial was designated a phase 2 trial. However, as also noted in the ICH guidelines, phase designation is often descriptive, not a set of requirements, and may not provide an adequate basis for classification, as some trials can occur in more than one phase. This trial may be a good example of one that spans phases 2 and 3.

Eric Winquist 2: On page 8 it should be stated that the study was approved by local ethics boards at each site.

Response: Appropriate text was added.

Eric Winquist 3: The trial is described as a noninferiority design. In such a design the noninferiority margin (#) should be clearly defined. The definition of # is stated in a very confusing manner and needs clarification: “we made the assumption that the change in hemoglobin for the darbopoetin alfa EDS regimen from baseline to Week 13 would be demonstrated to be greater that the placebo if the 95% CL for the difference in mean hemoglobin values between the EDS and QW regimens of darbopoetin alfa was not more that 0.75 g/dL.” Clearly the EDS regimen is not being compared to a placebo but to an active standard arm, and the choice of # should reflect this.

Response (added to the Methods section of the manuscript): We appreciate the referee’s concern regarding the definition of the non-inferiority margin. The non-inferiority margin for change in hemoglobin used in this study, 0.75 g/dL, is based on the concept of preserving 50% of the difference in the mean change in hemoglobin from baseline to week 13 in the active arm of previous placebo-controlled trials (references 3
and 5 in the manuscript). If the upper limit of the 95% CL for the difference in the mean change in hemoglobin between the QW regimen of darbepoetin alfa and the EDS regimen of darbepoetin alfa (QW – EDS) is not more than 0.75 g/dL, then the conclusion from this study will be that EDS of darbepoetin alfa is non-inferior to darbepoetin alfa administered QW and that the efficacy of EDS of darbepoetin alfa is greater than placebo.

**Eric Winquist 4:** The calculated sample size should be explained based on the # defined.

Response (added to the Methods section of the manuscript): Assuming that the difference in hemoglobin between the two treatment groups is 0.1 g/dL and that the standard deviation for the difference in the mean change in hemoglobin from baseline to week 13 between the two treatment groups is 2.6 g/dL, a total of 750 randomized subjects (375 subjects per treatment group) would provide 92% power to demonstrate non-inferiority of EDS to QW, with respect to a non-inferiority margin of 0.75 g/dL and a 1-sided t-test procedure with a Type I error rate of 5%.

**Eric Winquist 5:** It is unclear if an “as treated” analysis was done, as this may be more appropriate for a noninferiority design and the proportion of patients not completing the study was relatively high in both arms.

**Eric Winquist 6:** The “last value carried forward approach” used to analyze the primary endpoint should be described in the Methods section.

Response to both points: All of the efficacy analyses (hemoglobin endpoints) were pre-specified to be analyzed as intent-to-treat (i.e., as randomized) rather than “as treated”. Only the adverse events were analyzed “as treated”. We would like to clarify that the available data approach is not the same as the “as treated” dataset. Both available-data approach (with no imputations) and last value carried forward (LVCF) imputation approaches were used for the primary endpoint.

An abbreviated version of this language has been added to the Methods section of the manuscript.

**Eric Winquist 7:** Patients in the EDS arm had lower mean serum erythropoietin levels and received higher average weekly doses of darbopoetin; but fewer achieved the target hemoglobin level of >11 g/dL and had hematopoetic response, and more required transfusions. Yet the conclusion of the authors is that the EDS arm is noninferior based on the definition of noninferiority. This conclusion needs to be better justified.

Response: We’d like to note that while the baseline erythropoietin concentrations (EDS: 73.4 mU/mL vs. QW: 86.9 mU/mL) and average weekly darbepoetin alfa doses (EDS: 106.8 µg vs. QW: 98.2 µg) differ numerically, these differences are not necessarily clinically significant (we did not test for statistical significance). In particular, the dose of darbepoetin alfa was essentially the same, especially when corrected for weight (EDS: 1.5 µg/kg vs. QW: 1.4 µg/kg).

However, the changes in hemoglobin endpoints were similar, both for primary endpoint (change in hemoglobin from baseline to Week 13 of 0.9 g/dL for both groups) and secondary endpoints (proportion achieving hemoglobin level > 11 g/dL from baseline to
Week 13: 71% EDS vs. 76% QW, proportion with hematopoietic response from baseline to end of treatment: 84% EDS vs. 86% QW). We would also like to note that fewer patients in the EDS arm (not more) required transfusions (26% EDS vs. 29% QW, not significant). Given the minor differences in characteristics and dose, and an endpoint dataset that did not clearly favor one group over another, we feel confident in concluding noninferiority.

Minor Essential Revisions:

Eric Winquist 1: The last sentence of the Background sentence belongs in the Discussion.

Response: We have removed the last sentence of the Background.

Eric Winquist 2: In the Results and Consort diagram, patients randomized but not receiving treatment and reasons for this are not described.

Response: We have added to the Results section that there were a variety of reasons why patients were randomized but not treated, such as that the patient either delayed or did not have chemotherapy (5 patients) or withdrew consent (4 patients), with a variety of reasons for the remaining 9 patients (such as screening failure, patient was hospitalized, patient was on a different chemotherapy schedule, etc.).

Eric Winquist 3: Rates of transfusion are reported in the Discussion but not in the Results.

Response: In the interests of brevity, transfusion rates were depicted on Figure 5, which is cited in the Results section.

Discretionary Revisions:

Eric Winquist 1: It is unclear why tumor type was used as a stratification factor.

Response: As we have added to the Methods section, efficacy of ESAs may vary with type of chemotherapy, such as platinum-based therapies. Certain tumor types, such as lung, are more likely to be treated with platinum-based chemotherapy. We therefore stratified by tumor type to minimize the role that the chemotherapy agent(s) would affect the outcomes.

Eric Winquist 2: First sentence in Methods is difficult to understand and awkwardly written.

Response: To improve clarity, this content is now described in two sentences.
Minor Essential Revisions

*Xue Song 1: Methods in Abstract: The first sentence could be revised to include the treatment arms in the comparison, such as “This phase 2, 25-week, open-label study evaluated the noninferiority of extended dosing schedule versus weekly dosing schedule of darbepoetin alfa in patients with CIA.”*

Response: The sentence has been revised to include the information suggested.

*Xue Song 2: Provide the start and end month and year of when this clinical was conducted.*

Response: This information has been added to the Methods section under Study Design.

*Xue Song 3: 95% CL was first mentioned on page 8 but the full description of 95% CL was not given until page 11.*

Response: We appreciate the referee catching the error. The text has been changed accordingly.

*Xue Song 4: The last sentence of the first paragraph on page 11, “Analysis of individual strata with large sample sizes showed a similar lack of differences between treatment groups.” It would be interesting to list the individual strata that were examined.*

Response: We added text to the Results section indicating that strata examined included screening hemoglobin $< \text{or} \geq 10 \text{ g/dL}$ for each dosing schedule (QW, Q2W, or Q3W).

*Xue Song 5: The title of table 1 should be “Patient demographic and clinical characteristics.” It will be interesting to report the mean length of chemotherapy cycle in both treatment arms as chemotherapy cycle length was controlled for in the estimation of change in hemoglobin from baseline to Week 13 (page 11). It will also be interesting to report the chemotherapy cycle distribution in the EDS arm.*

Response: We have amended the table title. The analyses regarding chemotherapy cycle length and distribution have not been performed and thus these data are not available.

Xue Song 6: Figure 3. Is there a footnote for superscripts a & b?

Xue Song 7: Figure 5. Is there a footnote for superscript a in “Difference (95% CL)”?

Response: We thank the referee for catching this error. The text referred to was mistakenly removed from the submitted version. This text is now in the Figure Legends.

Discretionary Revisions

*Xue Song 1: The results section in the abstract can also include findings on transfusions since transfusion is a secondary endpoint.*

Response: We appreciate the suggestion and have revised the text accordingly.
Xue Song 2: Table 1-4. Can authors provide p values of statistical tests that compare the QW and EDS arms?

Response: In general, p-values for demographic and safety data are not typically calculated. We have provided p-values from prespecified analyses for key efficacy endpoints and have revised Table 2 (Hemoglobin Endpoints) and Table 3 (Change in FACT-F Score) accordingly.