Reviewer's report

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

Version: 1 Date: 5 October 2009

Reviewer: Eric Winquist

Reviewer's report:

The authors report the results of a randomized open-label trial comparing two dosing schedule of darbopoetin alfa in anemic cancer patients receiving chemotherapy.

Major Compulsory Revisions:

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.

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

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 than the placebo if the 95% CI for the difference in mean hemoglobin values between the EDS and QW regimens of darbopoetin alfa was not more than 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.

4. The calculated sample size should be explained based on the # defined.

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.

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

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.

Minor Essential Revisions:
1. The last sentence of the Background sentence belongs in the Discussion.
2. In the Results and Consort diagram, patients randomized but not receiving treatment and reasons for this are not described.
3. Rates of transfusion are reported in the Discussion but not in the Results.

Discretionary Revisions:
1. It is unclear why tumor type was used as a stratification factor.
2. First sentence in Methods is difficult to understand and awkwardly written.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.