March 4, 2008 – Responses to reviewers

Re: Manuscript revision

NRES-D-07-00218, “Significant impairment in immune recovery following cancer treatment”

Reviewer 1:
Abstract – Specify the study design and include 2-3 sentences on the data analysis methods: Information on study design and data analysis methods is added to the abstract.

At the end of the introduction, clarify the hypotheses: Hypotheses are restated and are furtherclarified.

Under the method section, clarify the study design: The study design is clarified and is added to the method section.

Under the section on participants, provide more information on the settings: More detailed information is added to the section describing the participants, and the rationale for the sample size is included.

More details on the data collection procedure …: Data collection procedure is now separate from the immune measurement section, and details on the data collection procedure are provided as recommended.

Link the data analysis methods to the hypotheses…: Data analysis section is substantially revised to clearly indicate how the data were analyzed to test the hypotheses of the study.

Reviewer 2:

Reviewer 2 pointed out many positive aspects of this paper. Only one recommendation was to **reduce the discussion of the association between immune markers, outcomes and advanced disease into a sentence in the Discussion section. Reviewer 1, however, thought that the discussion section was well written with supporting literature.**

Discussion about advanced cases is reduced to a minimum because the sample of this study does not include the advanced cases. However, some discussion related to advanced cases,
we believe, is highly appropriate to explain the potential implications of delayed immune recovery
or immune dysregulation, which typically become more apparent with advances of cancer stage.

Reviewer 3:

A recommendation is to add the actual percentages of subjects who have reached or exceeded the baseline values within each adjuvant therapy group under different time point:

Two tables (Table 3 and 4) are added to the result section for this purpose: One represented by each cancer adjuvant therapy and the other represented by each cancer stage.

No evidence or conceptual framework to support the two proposed hypotheses: The significance of this study can be further highlighted by the fact that there is a paucity of studies to provide clear evidence for hypotheses of this study. In one prior study, immune reconstitution was followed prior to stem cell mobilization, and at 1, 3, 6, 9, and 12 months post high-dose chemotherapy with stem cell rescue in patients with advanced breast cancer. These findings provide indirect evidence to support our hypotheses, which have been revised into three hypotheses. We included this information toward the end of introduction, followed by the description of revised hypotheses. This revision more accurately reflects what is tested in this study.

Issues related to the prediction model: We substantially revised the data analysis section to provide more detailed information about how the prediction models were set up. Accordingly, Tables 5-7 based on this prediction model were revised to provide the accurate information to the reader. We believe that this additional information would provide the capacity for interested researchers to duplicate similar studies.

How to assess the accuracy of those probabilities, sample size, model fit, and other statistical issues: Again, in the revised section of data analysis, we provide more details on many issues raised by the reviewer. About accuracy of the probabilities, detail in terms of estimation method and handling of missing values is added. As pointed out by the reviewer, determination of accuracy of estimates is not directly possible, but rather requires replication and/or some other model validation method. However, presentation of the standard errors associated with the estimates provides an indication of precision of estimates. We also include results of collinearity statistics, demonstrating no collinearity. In addition, we changed symbols and provided more in-depth explanation of estimated probabilities: We used symbols as appeared in the SAS GLIMMIX Procedure Guide showing derivation (SAS Institute, Inc. (2005). The GLIMMIX procedure, Carey, NC: SAS Institute, pp. 16-17 & 139). With respect to model fit, generalized linear mixed models do not have a model fit test such as the Hosmer-Lemeshow test available for “traditional” logistic regression models. We added a statement about examination of fit statistics. However, those fit statistics pertain only to evaluating the repeated measures covariance structure and cannot be used to evaluate fit across different (even nested) statistical models.

The results section needs to be strengthened… The results sections are reorganized and strengthened by highlighting important findings for each hypothesis. However, our goal is not to duplicate the same information available in the Tables. Three regimens of chemotherapy (AC, ATC, and ACT) are fairly well standardized in the institution where this study was conducted. We explored three regimens of chemotherapy on immune recovery, but the sample size was insufficient for statistical analyses. We added this statement in the result section for clarification. In the table presentation, a potentially confusing use of word “combined” is now changed to “chemo+radiotherapy” when appropriate.