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John A. Chabot, M.D., F.A.C.S.
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Dear Dr. Chabot:

As you know, Dr. Gonzalez sent a letter dated January 7, 2005, to Dr. Jack Killen at NCCAM. In it he outlined a number of concerns about questions asked by Dr. Killen at our meeting on December 13. As the Program Officer in NCCAM responsible for administering this grant, I am writing to you now in response to that letter, because it appears that Dr. Gonzalez seriously misinterpreted the motivation for and beliefs underlying Dr. Killen's questions to the group. As Dr. Wendy Smith indicated in correspondence with you prior to that meeting (copy enclosed for your convenience), two of the goals of the NIH team were to probe into the existing data, and to understand the rationale and specific plans for the future of the study. It is possible that Dr. Killen's style of questioning – which included both attempts to clarify points of uncertainty and also playing devil's advocate – may have led Dr. Gonzalez to conclude that he had "...a completely different agenda." (See his letter of January 7th.) We thought it important to clarify for you, as Principal Investigator of the study, key points raised in the letter in order to ensure that they are clearly articulated for the entire team, and so that the record is appropriately corrected.

Dr. Killen's questions were all grounded in an overall assessment of the study that included these points:

- The study is designed to compare survival resulting from two forms of treatment for advanced pancreatic cancer. The study is based on interesting and intriguing pilot data that clearly merited further investigation, given the poor prognosis for this disease. Based on these data, the study was originally powered to detect a doubling of median survival for patients on the pancreatic enzyme arm compared to control.

- There have been numerous and very difficult scientific, operational, and procedural challenges in carrying out this trial. These have been well documented and frequently discussed.

- The results of the trial, as contained in the most recent interim analysis, are both surprising (control arm) and disappointing (experimental arm), particularly in comparison with the historical data on which the protocol was based.

- As of the most recent interim analysis, the data appear to reject the null hypothesis (that the two treatments are equal) in favor of the control arm.

- In spite of everyone's best efforts, it appears as if the current design and implementation of the study may have resulted in accrual into the two study arms of patient populations that are not comparable. As a consequence, it is very difficult (if not impossible) to ascertain treatment effect with certainty.

- Given all of the challenges, the surprising outcomes, and the uncertainties about balance between the two arms, it is highly likely (if not certain) that reviewers of the data from this study will raise substantive and legitimate concerns about the comparability of the two populations. As a consequence, it is virtually certain that the controversy surrounding the study will not be settled by the data from it.

- It seems highly improbable that additional accrual of subjects into the study, as it is currently designed and being implemented, could result in a reversal of the current findings such that the null hypothesis is rejected in favor of the enzyme therapy arm. However, a formal futility analysis [or something equivalent, given that this is not a randomized trial] to verify or reject this presumption had not been carried out.

It seems to us that thinking about the future of this particular trial depends very much on whether or not this assessment is accurate. One of the most important lines of discussion centered on the question of whether it is plausible that we could see a reversal of the outcome seen in the interim analysis with additional accrual to the experimental arm, given the study's current design and implementation, and given the data that we have in hand. (This is the basis for our keen interest then and since in the futility analysis.) If the answer to that question is "yes", then it would be important to continue the study to its conclusion, which would be determined by a specific plan to a specific endpoint such as the stopping rules that we discussed. If the answer is no, then there would be little point in additional accrual to this trial, as it is designed.

The December 13 discussion with the team was very illuminating in that nothing materially altered this assessment. With respect to the specific matters raised in Dr. Gonzalez' letter, we will make only two brief comments.

- We discussed at considerable length his concerns about the probable accrual of patients unable to comply fully with the nutrition arm of the protocol. It was our impression that everyone in the room basically agreed that, despite best efforts, there is in fact, reason to be concerned about this issue, and that it clouds interpretation of the data. Even if we assume, however, that this is the explanation for the disappointingly poor outcome of patients on the nutrition arm, accrual of 15 or 20 additional patients to the nutrition arm of this comparative study, as it is designed and currently being implemented, would only be appropriate if there is a chance that the interim results would change. It is our hope that the "futility analysis" and/or stopping rules, which we understand that Dr. Wei Yann is developing for consideration by the team, will be helpful in this decision.

- There may, indeed, be endpoints other than survival that are worth examining – e.g., quality of life. This was also mentioned during the December 13 discussion, although not pursued. Pursuing this avenue of interest, however, should follow a specific hypothesis and a specific study plan, which the current study lacks.

In conclusion, let us say that we have tremendous respect and admiration for the team that has worked with extraordinary skill and care on this study. We are also disappointed that the current study has not yielded a clear answer to the question that it was designed to answer – in spite of the team's hard work and everyone's very best efforts. Our primary concern at this juncture is that we proceed with a scientifically and ethically rigorous, defensible, and transparent plan that is based on all that we know and have learned to date, and that is, first and foremost, aimed at giving patients with pancreatic cancer and their care providers clear and unambiguous information as soon as possible.

Sincerely yours,

Linda W. Engel
Special Assistant to the Director, for Program Development

Enclosure

Cc:
Dr. Karen Antman
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Ms. Michelle Gabay
Dr. Nicholas Gonzalez
Dr. Victor Grann
Dr. Linda Isaacs
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