Gynecologic Cancer Intergroup
Harmonization Committee, Statistical Section
Wyndham Orlando Resort
Orlando, Florida
Friday May 29, 2009

Meeting Minutes

Participants: Garnet Anderson, Mark Brady, Val Gebski, Sally Hunsberger, Jim Paul, Wendi Qian, Alexander Reuss, Dongsheng Tu, and Kathryn Winter.

The meeting of the Statistical Section of the GCIG Harmonization Committee was called to order on Friday, May 29, 2009 at the Wyndham Resort, Orlando, Florida. Mark Brady indicated that there were primarily three items on the agenda for discussion: topics for future meetings, Reporting results from non-inferiority trials, and approaches to efficient phase III trial design.

1. **Topics for future meetings**: Topics suggested for future meetings include:
    a. Constructing a standardized list of "key" prognostic covariates for patients diagnosed with ovarian cancer and typical value labels for each covariate. Groups would then be encouraged to capture data in future trials in a fashion that permits translating patient data into this standardized format.
    b. It was proposed that the Statistical Section of the GCIG Harmonization Committee prepare a document explaining the various procedures used by the Groups for patient-level and trial-level unblinding.

3. **Reporting results from non-inferiority trials**: Val Gebski presented some of the challenges in analyzing and presenting the results from non-inferiority trials, like the recently completed Calypso Trial. He emphasized the shortcomings of conducting pure intention-to-treat analyses for such trials. He concluded that while it may be reasonable to conduct the primary analyses based on intention-to-treat, he recommended that additional as-treated analyses be undertaken to uncover potentially informative associations.

4. **Approaches to efficient phase III trial design:** Sally Hunsberger presented an interesting approach to improving the efficiency of phase III trials. First, she reviewed the shortcomings of single-arm phase II trials. Specifically, if the bar for activity in a single-arm phase II trial is set too low, due to uncertainty or intra-trial variability in the historical data, then the type I error will be greater than intended and hence too many inactive treatments will be earmarked for phase III evaluation. On the other hand, if the bar is set too high, the power of the study will be reduced and therefore some active treatments will missed. She argued that randomization was essential in phase II trials to ensure that type I/II errors are properly controlled. Therefore, it was reasonable to consider integrating the phase II evaluation into the phase III trial.

Using simulation she compared three approaches to phase II/phase III drug development. The first approach involved a sequence of randomized phase II and phase III studies. The second approach integrated the phase II and phase III trial into a single study and the decision to proceed to the phase III study was based on an interim futility analysis of overall survival. The third approach was similar to the second, but the decision to proceed to the phase III study was based on an interim futility analysis of progression-free survival.

Based on the results of her simulations, Sally concluded: a) While single-arm studies may appear to use fewer patients, if the null bar in set too low, the expected sample size for the sequential phase II and III trials tend to be much larger than the integrated approach. If the bar is too low, effective treatments are missed. b) If it can be assumed that clinical progression is an intermediate event to death, then using PFS rather than overall survival for interim futility analysis can reduced the overall expected sample size and the expected study duration in a integrated randomized phase II/III trial, when the null hypothesis is true. On the other hand, when the alternative hypothesis is true neither the expected sample size nor expected duration of the study is increased substantially.

The integrated approach using PFS for interim futility analysis was used in the GOG-182/ICON5 trial. It has also been used in several other trials planned by the MRC. See for example, Parmar et al, JNCI 100:1204-1214 2008, and Barthel et al, Trails, 10:21, 2009.

The meeting was adjourned at 5:00 pm.