Meeting Minutes
June 2, 2011

Gynecologic Cancer Intergroup
Harmonization Committee, Statistical Subcommittee
Hilton Hotel
Chicago, Illinois, USA

Participants: Mark Brady, Val Gebski, Byung-Ho Nam, Jim Paul, Masahiro Takeuchi Dongsheng Tu, Wendi Qian, Alexander Reuss, Kathryn Winter,

The meeting of the Statistical Section of the GCIG Harmonization Committee was called to order at 4:30 pm, June 2, 2011 at the Hilton Hotel in Chicago, Illinois USA. There were primarily four items on the agenda for discussion:

1. Define a list of "key" prognostic variables and values for ovarian cancer trials. The purpose of this list is to facilitate data sharing for meta-analyses after the trial has been completed.

a. First-line treatment trials – There were no changes made to the current proposed list (See Attachment I).
b. Second-, third- line treatment trials – Time did not permit a discussion of key variables for second line treatment trials.

2. Clinical Trials in Rare Diseases. Prior to this meeting Jim Paul identified publications concerning the design of treatment trials in rare diseases. At the meeting, he reviewed the primary concepts in each publication. The committee members discussed their approaches for designing these trials and developed recommendations for designing future phase III trials evaluating treatments for rare diseases. (See Attachment II).

3. Topic for the next meeting: Design considerations for biomarker-based phase II treatment trials.

4. Statistical Topics proposed for future meetings include:

a. Dose intensity (Ruess).
b. The PFS/OS endpoint controversy for phase III front-line treatment trials (Brady).
c. Biomarker driven trials.(Paul).

The meeting was adjourned at 6:00 pm.

(attachments below)

Attachment I

I. Standard Baseline Key Variables for First-line Trials in Epithelial Ovarian Carcinoma:

1. Age – Years from birth to date of randomization/registration.

2. Performance Status –
   0 – Fully active,
   1 – Restricted in physically strenuous activity, but able to carry out light work,
   2 – Ambulatory and capable of all self care, but unable to carry out work activities, Up and about more than 50% of waking hours.
   3 – Capable of limited self care, confined to bed or chair > 50% or waking hours,
   4 – Completely disabled, cannot carry on self care, totally confined to bed or chair.

3. FIGO Stage – I, II, III, IV, Ia, Ib, Ic, IIa, IIb, IIc, IIIa, IIIb, IIIc, unknown.

4. Surgically assessed extent of residual disease: None, Microscopic disease only, gross residual disease. The study may opt to distinguish between patients with gross residual disease where no lesions have a maximum diameter larger than 1 cm and those with at least one lesion larger than 1 cm.

5. Ascites (> 500 cc): Yes, no, unknown.

6. Malignant pleural effusion: Yes, no, suspicious, unknown.

7. Malignant ascites or cytologic washings: Yes, no, suspicious, unknown.

7. Histology: papillary serous, clear cell, mucinous, endometrioid, mixed epithelial, transitional cell, small cell, undifferentiated or unspecified adenocarcinoma, other, unknown.

8. Grade: 1, 2, 3, no grade (eg, clear cell)

9. Lymph node involvement:
   a. Pelvic lymphadenectomy performed: Yes, no, unknown.
   b. Para-aortic lymphadenectomy performed: Yes, no, unknown.
   c. If either a pelvic or para-aortic lymphadenectomy was performed, were any nodes with metastatic disease identified?

10. CA-125 (and upper limit normal): Value in IU. (Jim to look at prognostic value in SCOTROC trial).

11. Serum albumin

12. Alkaline phosphatase.

II. For Early Stage (I, II) Disease Only:

Tumor capsule ruptured: Yes, no, unknown.

Attachment II

Phase III Trial Designs for Rare Diseases

Premise: The purpose of a phase III trial is to provide compelling evidence to persuade reasonable clinicians and their patients to either adopt or reject a new treatment or intervention. The degree to which a study provides compelling evidence to both the investigators involved in the study and those external to the study is one measure of a study's success.

Consensus points:

1. Adequately powered, randomized controlled trials remain the preferred design for providing the best clinical evidence concerning a treatment's activity and risks for toxicity.

2. In order to conduct studies in rare diseases, collaboration among investigators or groups of investigators is preferred, albeit often difficult. For some rare diseases it may be necessary to consider collaborations among specialized centers, where a certain critical expertise is available.

3. When a randomized controlled clinical trial can not be completed in a reasonable timeframe, some alternatives can be considered.

    a. A review of the literature indicated that there have been only a few alternative designs proposed specifically for rare diseases. One utilized a Bayesian approach to incorporating historical trial data (Tan et. al. 2008), and the second utilized a frequentist approach and repeated response assessments (Honkanen et. al. 2001). While both of these designs are interesting, neither one garnered strongly support from the committee members. Bayesian designs provide a mechanism for formally incorporating historical data into the design, but they also involve subjective prior beliefs which may not be universally accepted.

    b. Before entirely abandoning the effort to conduct a randomized trial investigators might consider:

        i. Judiciously relaxing the type I error. This will effectively reduce the required sample size. However, careful consideration needs to be given to the consequences of erroneously concluding that an inferior treatment and potentially a more toxic treatment is more effective than the standard treatment. Since, conducting confirmatory trials in a rare disease are formidable; utilizing one-tail 5% type I error in a phase III trial may be considered acceptable. Note that this is not as lenient as the type I error rates proposed for designing

randomized phase II trials, which may be as large as 20% (Rubinstein, 20XX). The purpose of those studies is to simply identify potentially active treatments that will be further evaluated in subsequent trials. Since phase III trials in rare diseases are very challenging to conduct, and therefore they are unlikely to be confirmed by a second study, the consequences of committing type I error must be considered serious.

ii. Utilizing an optimistic alternative hypotheses (ie increasing type II error). Designing trials with adequate power to detect treatments that triple the time to progression, or double the time to death may only be possible. This may be justifiable when the disease is grave and a favorable response is critical. When this option is selected, then the focus of interpreting the final result should emphasize the confidence interval (frequentist design) or the credible interval (Bayesian design) rather than hypothesis tests and p-values.

c. Single-arm study designs for rare diseases can be considered when:
   i. The disease is very grave and the documented probability of response is very low (ie less than 15%).
   ii. No standard treatment exists. However, this is not to be confused with the case where the standard of care is no treatment (surveillance). Also, this does not include rare diseases where there is more than one standard of care, and clinical investigators are divided on the preferred standard of care. In that case a randomized trial may be needed to compare the various standards of care. This is an important first step, since the interpretability of any subsequent trials will depend on the rationale for selecting the standard (reference) treatment.
   iii. Robust historical data is available, which suggests that after adjusting for potential prognostic factors, trial-to-trial variation is relatively small. (An example is the advanced stage mucinous ovarian cancer meta-analysis and a counter-example is the advanced stage clear cell cancer of the ovary meta-analysis, MacKay et al., 2010).