Re: New Guidelines to Evaluate the Response to Treatment in Solid Tumors (Ovarian Cancer)

The Gynaecologic Cancer Intergroup (GCIG) believes that definitions for response and progression of ovarian cancer according to serum CA 125 levels should be incorporated into ovarian cancer clinical trial protocols for relapse therapy. Although the GCIG is convinced of the value of the definition of progression that incorporates both Response Evaluation Criteria in Solid Tumors (RECIST) and CA 125 criteria and which should be used to define date of progression *(1,2)*, the response definition as defined by Rustin *(3)* could benefit from further simplification. On the basis of the available data and extensive discussions among the cooperative groups within the GCIG, we recommend that the following definition of response be used in ovarian cancer trials so that response can be measured by either RECIST or CA 125 criteria. If the response is evaluable by both criteria, then the date of response will be the date of the earlier of the two events.

> A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate CA 125 responses accurately, the following rules apply: 1) Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample. 2) Variations within the normal range of CA 125 levels will not interfere with the response definition. We recommend that, in an ideal situation, CA 125 measurements be taken at specific time intervals. The first sample would be collected within 2 weeks before treatment is started, and later samples would be collected at intervals of 2–4 weeks during treatment and at intervals of every 2

or 3 months during follow-up. For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme. Patients are not evaluable by CA 125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

This CA 125 response definition has been produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA 125 response results from both treatments, and it should be clearly stated that CA 125 cannot distinguish between the effects of each treatment. To calculate response rates in protocols, an intent-to-treat analysis should be used that includes all patients with an initial CA 125 level of at least twice the upper limit of normal as eligible and evaluable. In addition to calculating response rates in protocols, it is advisable to record those patients who have both a CA 125 response and whose CA 125 level falls to within the normal range *(4)*.

Gavin Shreeves supervised an independent validation of this definition by Justine Rochon for the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO; Munich, Germany), Desiré Paraiso for Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO; Paris, France), and Margot Osinski for The Australian and New Zealand Gynaecological Oncology Group. An example of its use can be seen on the Gynaecologic Cancer Intergroup Web site (http://ctep.info.nih.gov/resources/gcig/ index.html).

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Notes

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