
**Re: New Guidelines to Evaluate
the Response to Treatment in
Solid Tumors [Ovarian Cancer]**

We read with much interest the article by Therasse et al. (1) on the new Response Evaluation Criteria in Solid Tumors Group (RECIST) in the Journal. In the RECIST, the definition of progression is based on the evaluation of measurable and nonmeasurable disease. However, it is our experience that, in many randomized trials of the first-line treatment of ovarian cancer, in which progression-free survival is often the primary end point, investigators start

second-line treatment based on an increase in serum CA 125 levels only, without clinical evidence of progression. This practice has led to confusion in establishing the date of progression, since such cases, in which treatment is initiated before objective progression has been documented, are handled in variable ways by different groups. Some groups count these patients as having progressive disease, others censor them, and others ignore treatment before disease progression altogether.

In an effort to address this issue in a consistent manner, a working group of the Gynecologic Cancer Intergroup has developed definitions of CA 125 progression to complement the definitions of objective disease progression for use in first-line chemotherapy trials in ovarian cancer. The definitions of CA 125 progression are based on the well-known and validated definitions of progression in ovarian cancer using serum CA 125 levels (2). The published data support the concept that, after first-line therapy, doubling in CA 125 from the upper limit of normal reliably predicts objective progression (lead time varies from 0 to 12 months; median, 63 days). For those patients whose CA 125 never fell to the normal range, a doubling from the nadir has been shown to predict progression among such patients treated at the Mount Vernon Hospital with a false-positive rate of <2% (Rustin G: personal communication).

The proposed definitions of progression in Table 1 consider three patient groups, according to their serum CA 125 behavior during first-line therapy. A patient may be declared to have progressive disease on the basis of either the objective RECIST criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the two events if both are documented. Since it was recognized that the timing of investigations during first-line therapy and subsequent follow-up may also influence the date of progression-free survival in clinical trials, we propose that serum CA 125 levels be obtained on day 1 of each chemotherapy cycle, 4 weeks after the last course, thereafter every 3–4 months for the first 36 months, every 6 months from month 37–60, and every year from 5 years after the primary diagnosis.

It should be emphasized that these definitions of progression are intended

Table 1. Definition of progression after first-line therapy in ovarian cancer as proposed by the Gynecologic Cancer Intergroup*

		Patient group (definitions below)		
		A	B	C
Measurable/nonmeasurable disease	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition; 1)			
	or Any new lesions (measurable or nonmeasurable) Date PD: date of documentation of increase or new lesions			
		and/or†		
		A	B	C
CA 125	CA 125 $\geq 2 \times$ UNL documented on two occasions‡ Date PD: first date of the CA 125 elevation to $\geq 2 \times$ UNL	CA 125 $\geq 2 \times$ nadir value on two occasions* Date PD: first date of the CA 125 elevation to $\geq 2 \times$ nadir value		As for A

*UNL = upper normal limit; PD = progressive disease.

†A. Patients with elevated CA 125 pretreatment and normalization of CA 125 (~60% of all new patients); B. Patients with elevated CA 125 pretreatment, which never normalizes (~30% of all new patients); C. Patients with CA 125 in normal range pretreatment (~10% of all new patients).

‡Repeat CA 125 any time, but normally not less than 1 week after the first elevated level. CA 125 levels sampled within 4 weeks after surgery, paracentesis, or administration of mouse antibodies should not be taken into account.

for the specific context of first-line therapy studies. We acknowledge that further work is needed to reach a consensus on the place of CA 125 in defining response and progression in the circumstance of phase II trials of new drugs in relapsed ovarian cancer, which is the primary setting for which the RECIST criteria were developed.

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REFERENCES

- (1) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; 92:205–16.
- (2) Rustin GJ, Nelstrop AE, Tuxen MK, Lambert HE. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. *Ann Oncol* 1996;7:361–4.

NOTES

The GCIG (Gynecologic Cancer Intergroup) has representatives of the EORTC–GCCG (European Organization for Research and Treatment of Cancer–Gynaecological Cancer Cooperative Group), MRC (Medical Research Council), NCIC CTG (National Cancer Institute Canada Clinical Trials Group), NSGO (Nordic Society of Gynaecologic

Oncology), AGO (Arbeitsgemeinschaft Gynäkologische Onkologie), NCI-US (National Cancer Institute United States), GINECO (Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens), GOG (Gynecologic Oncology Group), COSA (Clinical Oncology Society of Australia), RTOG (Radiation Therapy Oncology Group), SGCSG (Scottish Gynaecological Cancer Study Group) and the SWOG (South-West Oncology Group).

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