Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG)

Gordon John Sampson Rustin, MD, MSc, FRCP, Ignace Vergote, MD, PhD,† Elizabeth Eisenhauer, MD,‡ Eric Pujade-Lauraine, MD,§ Michael Quinn, MBBCh, MSc, MRCP,|| Tate Thigpen, MD,¶ Andreas du Bois, MD, PhD,** Gunnar Kristensen, MD, PhD,†† Anders Jakobsen, MD,‡‡ Satoru Sagae, MD, PhD,§§ Kathryn Greven, MD,|||| Mahesh Parmar, MD,¶¶ Michael Friedlander, MD, PhD,*** Andres Cervantes, MD, PhD,††† and Jan Vermorken, MD, PhD‡‡‡*

Abstract: The Gynecological Cancer Intergroup (GCIG) has previously reached consensus regarding the criteria that should be used in clinical trial protocols to define progression-free survival after first-line therapy as well as the criteria to define response to treatment in recurrent disease using the serum marker CA 125 and has specified the situations where these criteria should be used. However, the publications did not include detailed definitions, nor were they written to accommodate the new version of Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) now available. Thus, we recommend that the definitions described later in detail are incorporated into clinical trial protocols to maintain consistency. The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (Pujade-Lauraine, personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents.

Key Words: CA 125, Ovarian cancer, Response, Progression, RECIST, Clinical trials

Received August 2, 2010.
Accepted for publication November 16, 2010.

(*Int J Gynecol Cancer* 2011;21: 419–423)

The Gynecological Cancer Intergroup has previously reached consensus regarding the criteria that should be used in clinical trial protocols to define progression-free survival after first-line therapy[1] as well as the criteria to define response to treatment in recurrent disease[2] using the serum marker CA 125, and have specified the situations where these criteria should be used (Table 1). However, the publications did not include detailed definitions nor were they written to accommodate the new version of Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) now

*Mount Vernon Hospital, Northwood, UK; †University Hospital Leuven, Leuven, Belgium; ‡NCIC Clinical Trials Group, Kingston, Ontario, Canada; §Hopital Hotel Dieu, Paris, France; ||Royal Women's Hospital, Melbourne, Australia; ¶University of Mississippi School of Medicine, Jackson, MS; **Dr Horst-Schmidt-Klinik, Wiesbaden, Germany; ††Norwegian Radium Hospital, Oslo, Norway; ‡‡Vejle Hospital, Vejle, Denmark; §§Sapporo Railway Hospital, Sapporo, Japan; ||||Wake Forest University Medical Center, Winston Salem, NC; ¶¶MRC Clinical Trials Unit, London, UK; ***Prince of Wales Cancer Centre, Randwick, NSW, Australia; †††Hospital Clínico, University of Valencia, Valencia, Spain; ‡‡‡Antwerp University Hospital, Edegem, Belgium.

Address correspondence and reprint requests to Gordon John Sampson Rustin, MD, MSc, FRCP, Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex HA62RN, UK.
E-mail: grustin@nhs.net.

ISSN: 1048-891X
DOI: 10.1097/IGC.0b013e3182070f17

TABLE 1. GCIG recommendations for CA 125 criteria for response and progression in various clinical situations

	Use Recommended by GCIG	Not Standard and Needs Further Validation	Not Recommended by GCIG
First-line trials	CA 125 progression		Ca 125 response
Maintenance or consolidation trials		CA 125 response and progression	
Relapse trials	CA 125 response and progression		

available.[3] Thus, we recommend that the definitions described later in detail below are incorporated into clinical trial protocols to maintain consistency. The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (Pujade-Lauraine, personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents.

The GCIG recommends that for trials of relapsed ovarian cancer, the following definition for response according to CA 125 be used in addition to the updated RECIST 1.1[3] response criteria.

EVALUATION OF RESPONSE ACCORDING TO CA 125

Definition of Response

A CA 125 response is defined as 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 the reference range and within 2 weeks before starting the treatment.

To calculate CA 125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA 125 levels will not interfere with the response definition.
- 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 (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA 125 response results from both treatment modalities. CA 125 cannot distinguish between the effects of the 2 treatments.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response, 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 the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA 125 response and whose CA 125 level falls to within the reference range can be classified as CA 125 complete responders. In Tables 2 and 3 where CA 125 is stated as normalised or normal, means within the reference range. Patients who have a fall of CA 125 to within the reference range but whose initial CA 125 was less than twice the upper limit of the reference range have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

Evaluation of Response According to CA 125 in Patients Receiving First-Line Therapy

The CA 125 response definition was developed to evaluate response to chemotherapy in patients with recurrent ovarian cancer. If the patient has had combined modality therapy as part of their first-line therapy (eg, surgery and chemotherapy), CA125 response may be due to both or either treatments, and it should be clearly stated that CA125 cannot distinguish between the effects of the 2 treatments. It should be also be noted that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA 125 must be within the reference range.

Evaluation of Response According to CA 125 in Patients Receiving Maintenance or Consolidation Therapy

Patients whose CA 125 is greater than twice the upper limit of the reference range when they start maintenance or consolidation therapy can be evaluated using the GCIG CA 125 response definition. However, it should be noted that there are no data to validate the implications of achieving CA 125 response in this setting with respect to progression-free or overall survival. To prevent the prior therapy from interfering with the response assessment, we recommend that 2 pretreatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA 125, there should be no more than a 10% fall in CA 125 between the 2 pretreatment samples. The sample closest in time to the test therapy should be considered the pretreatment sample.

TABLE 2. Evaluation of best overall response in patients *without* initial measurable disease and who are evaluable by CA 125

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Evaluation of Best Overall Response in Patients *Without* Initial Measurable Disease and Evaluable by CA 125

CA 125 may be used to evaluate response in patients without initial measurable disease either because no measurable disease is evident on radiological imaging or because appropriate imaging has not been performed as demonstrated in Table 2.

Evaluation of Best Overall Response in Patients *With* Initial Measurable Disease and Who are Also Evaluable by CA 125

A report that combines both CA 125 and RECIST 1.1 criteria is likely to include patients who are measurable by one or both of the criteria and who may have events at different time points. It should be determined according to Table 3. In patients who have measurable disease by both

TABLE 3. Best overall response in patients with measurable disease and who are also evaluable by CA 125

Target Lesion*	Nontarget†	New Lesion	CA 125	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary end point
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New >28 days from CA 125 PR‡			PR	PR	
SD§	Non-PD	No	PR	PR	
SD§	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New ≤28 days From CA 125 PR‡			PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
‡Patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA 125 response.
§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

TABLE 4. Example of reporting RECIST, CA-125, and combined response

	CA 125 Response			
RECIST	**Yes**	**No or PD**	**N/E**	**Total RECIST**
CR*	***4***	0	0	*4*
PR	***3***	*1*	*1*	*5*
SD	**3**	12	1	16
PD	0	8	2	10
NE	**3**	5	2	10
Total CA 125	**13**	26	6	Total entered = 45

In the above example, the RECIST 1.1 response rate is 9 (25.7%) of 35 RECIST 1.1 evaluable patients, the CA 125 response rate is 13 (33%) of 39 CA 125 evaluable patients, and the combined overall response rate (either RECIST or CA 125 response) is 15 (35%) of 43.

*RECIST 1.1 includes normalization of CA 125 to achieve CR (Table 3).

Bolded numbers, CA 125 responders; bolded and italicized numbers, both RECIST and CA 125 responders; italicized numbers, RECIST responders.

criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used. In the combined assessment of CA 125 and RECIST 1.1 response, the following algorithm applies when determining the best overall response. If patients have progressive disease (PD) according to RECIST 1.1 within 28 days of CA 125 response, they are classified as having PD. If the PD according to RECIST 1.1 is longer than 28 days before or after the CA 125 response, they are classified as having partial response. Patients whose best response according to RECIST 1.1 is stable disease but who have a CA 125 response are classified as CA 125 responders.

REPORTING OF RESPONSE ACCORDING TO BOTH RECIST 1.1 AND CA 125 CRITERIA

Responses should be reported separately for both RECIST 1.1 and CA 125 response as shown in the hypothetical example in Table 4.

Definition of Progression on Therapy and Recurrence After Therapy According to CA 125

Progression (PD) is conventionally defined according to RECIST 1.1 but can also be based on serum CA 125 (defined below). However, in assigning the date of progression, PD by objective change in tumor size should always take precedence over CA 125 should it occur first. If measurable disease is reducing in size during treatment but the CA 125 results suggest progression (as defined below), the patient should continue to receive protocol treatment. If measurable disease is stable but CA 125 indicates confirmed progression over at

TABLE 5. Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG Subcategorized Group	RECIST Measurable/Nonmeasurable Disease		CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of diameters (RECIST 1.1 definition)	A N D	CA 125 ≥ 2 × ULRR documented on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × ULRR
	or		
	Any new lesions (measurable or nonmeasurable)	/	
	or		
	Unequivocal increase in nontarget disease		
	Date of PD: date of documentation of increase or new lesions		
B	As for A	O R	CA 125 ≥ 2 × nadir value on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × nadir value
C	As for A		As for A

GCIG groups A, B, and C defined above.

CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account.

*Repeat CA 125 any time but normally not less than 1 week after the first elevated CA 125 level.

ULRR, upper limit of response range.

least 4 weeks, some protocols may advise changing protocol treatment, unless there is the possibility that the therapy could be slowing the rate of rise of CA 125. If patients are having routine CA125 measurements as part of follow-up, the date of progression is likely to be several months earlier than symptoms or signs of progression develop.[6] Therefore, when categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined (CA 125 alone, CA125 and symptoms, and RECIST). Protocols will need to specify that these data have to be collected.

EVALUATION OF PROGRESSION ACCORDING TO CA 125

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125 according to the following criteria and Table 5:

A. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart *or*
B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart *or*
C. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have PD on the basis of either the objective RECIST 1.1 criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

REFERENCES

1. Vergote I, Rustin GJS, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment in solid tumours (ovarian cancer). *J Natl Cancer Inst*. 2000;92:1534–1535.
2. Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 2004;96:487–488.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
4. Taylor PT, Haverstick D. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 2005;97:151; author reply 152.
5. Rustin GJS. Response: Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 2005;97:152.
6. Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05-EORTC 55955): a randomised trial. *Lancet*. 2010;376:1155–1163.