

CA 125 definitions agreed by GCIG November 2005

The GCIG has agreed criteria for defining response and progression of ovarian carcinoma which use the serum marker CA 125, and the situations where these criteria should be used. It is recommended that the appropriate definitions described in detail below are cut and pasted into clinical trial protocols. The GCIG requests that data from all trial centers using these definitions is made available to trial centers associated with the GCIG so that continual validation and improvement can be accomplished.

CLINICAL SITUATIONS WHERE CA 125 CRITERIA FOR RESPONSE AND PROGRESSION AS DEFINED BELOW ARE RECOMMENDED BY THE GCIG

	USE RECOMMENDED BY GCIG	NOT STANDARD AND NEEDS FURTHER VALIDATION	NOT RECOMMENDED BY GCIG
FRONT LINE TRIALS	CA 125 PROGRESSION		CA 125 RESPONSE
MAINTENANCE OR CONSOLIDATION TRIALS		CA 125 RESPONSE AND PROGRESSION	
RELAPSE TRIALS	CA 125 RESPONSE	CA125 PROGRESSION	

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 standard RECIST response criteria.

EVALUATION OF RESPONSE ACCORDING TO CA 125

Definition of response. 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.

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 normal 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 HAMA^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA 125 response results from both treatments modalities. CA 125 cannot distinguish between the effects of the two treatments.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response rates, 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, as a separate analysis, those patients who have both a CA 125 response and whose CA 125 level falls to within the normal range, can be classified as CA 125 complete responders. Patients who have a fall of CA 125 to within the normal range but whose initial CA 125 was less than twice the upper limit of normal, 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 maintenance or consolidation therapy.

Patients whose CA 125 is greater than twice the upper limit of normal when they start maintenance or consolidation therapy can be evaluated according to the GCIg CA 125 response definition. It should be noted that there is no data to validate response evaluation in this situation. To prevent the prior therapy interfering with the response assessment the following requirement is recommended. Two pre-treatment 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 must be no more than a 10% fall in CA125 between the two pretreatment samples. The sample closest in time to the test therapy should be considered the pre-treatment sample.

Evaluation of response according to CA 125 in patients receiving first line therapy.

The CA 125 response definition was produced to evaluate relapse therapy. If assessing therapy that includes two treatment modalities (eg surgery and chemotherapy), any CA125 response is a result of both treatments, and it should be clearly stated that CA125 cannot distinguish between the effects of the two treatments. It should be remembered 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 normal range.

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 can be detected or because appropriate scans have not been performed.

CA 125	Non-Target 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 not 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	

#Non-target lesions include ascites and peritoneal thickening, which are not measurable according to RECIST

*Unequivocal progression in non-target lesions may be accepted as disease progression

EVALUATION OF BEST OVERALL RESPONSE IN PATIENTS WITH INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA 125

A report that combines both CA 125 and RECIST criteria, is likely to include patients that are measurable by one or both of the criteria, who may have events at different time points. In patients that are measurable by both criteria the date of response will be the date of the earlier of the two events. The following rules apply when determining the best overall response. If patients have PD according to RECIST within 28 days of CA 125 response they are classified as PD. If the PD according to RECIST is > 28 days before or after the CA 125 response they are classified as PR. Patients whose best response according to RECIST is SD but who have a CA 125 response are classified as CA 125 responders.

BEST OVERALL RESPONSE IN PATIENTS WITH INITIAL MEASURABLE DISEASE AND EVALUABLE BY CA 125, COMBINING BOTH CRITERIA

Target Lesion~	Non Target #	New Lesion	CA 125	Overall Best Response	Best RECIST response for this category also requires it to be confirmed and maintained for at least 28 days
CR	CR	No	Normal	CR	
CR	Non CR Non PD	No	Not PD	PR	
CR	CR	No	PR not normal	PR	
PR	Non PD	No	Not PD	PR	
NE	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	No	Not PR or PD	SD	
PD or New ≤ 28 days from CA 125 PR*			PR	PD	
PD	Any	Yes or No	Any	PD	
NE	PD	Yes or No	Any	PD	
NE	Any	Yes	Any	PD	
NE	Any	Yes or No	PD	PD	

see text above

~ target lesions include up to 10 measurable lesions as defined by RECIST

non-target lesions include ascites and peritoneal thickening which are not measurable according to RECIST

* patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA 125 response

REPORTING OF RESPONSE ACCORDING TO BOTH RECIST AND CA 125 CRITERIA

Responses should be reported separately for each criteria as shown below:

Criteria:	RECIST	CA125		Best Overall ^c
		Only	All CA 125 Evaluable ^b	
CR (%)	4 (11.4%) ^a	4 (40.0%) ^d	8 (19.0%) ^d	8 (17.8%)
PR (%)	5 (14.3%)	4 (40.0%)	6 (14.3%)	9 (20.0%)
SD (%)	16 (45.7%)	2 (20.0%)	20 (47.6%)	18 (40.0%)
PD (%)	10 (28.6%)	0 (0.0%)	8 (19.0%)	10 (22.2%)
Unknown (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Evaluable	35 (100.0%)	10 (100.0%)	42 (100.0%)	45 (100.0%)
Non-Evaluable	10	3		- ^e

a. RECIST includes normalization of CA125 to achieve CR (see best overall response table).

b. Includes all patients who are evaluable by CA125, either alone, or in combination with other evidence of disease.

c. Includes all evaluable patients in the study, regardless of method for assessing response (see best overall response table).

d. Includes all patients who had both a CA 125 response and their CA 125 level falls to within the normal range.

e. This column only includes eligible patients, i.e. evaluable by at least one of the criteria, therefore cell blank.

Definition of Progression on first line therapy and Recurrence after first line therapy according to CA 125.

Progression is defined according to RECIST but can also be based upon serum CA 125 (defined below) but tumour measurements should take precedence over CA 125. If measurable disease is shrinking during treatment, but the CA 125 indicates progression (as defined below) the patient should continue to receive protocol treatment. If measurable disease shows stable disease but CA 125 indicates progression after a minimum of 3 courses of chemotherapy, protocol treatment should be changed. If the GCIG definition based on CA 125 is used to define progression after relapse therapy it should be noted that it has not been validated.

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:

- A. Patients with elevated CA-125 pretreatment and normalisation of CA-125 must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart **or**
- B. Patients with elevated CA-125 pretreatment, which never normalises must show evidence of CA-125 greater than, or equal to, two times the nadir value on two occasions at least one week apart **or**
- C. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than, or equal to, two times the upper normal limit on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one 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 HAMA^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

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

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

GCIG subcategorized group	RECIST Measurable/non-measurable disease	CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or non-measurable) Date PD: date of documentation of increase or new lesions	CA 125 $\geq 2 \times$ ULN documented on two occasions # Date of PD: first date of the CA 125 elevation to $\geq 2 \times$ ULN
B	As for A	CA 125 $\geq 2 \times$ nadir value on two occasions # Date of PD: first date of the CA 125 elevation to $\geq 2 \times$ nadir value
C	As for A	As for A

A
N
D
/
O
R

GCIG groups A, B & C defined above.

Repeat CA 125 any time, but normally not less than 1 week after the first elevated CA 125 level. CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA^{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.

1. Therasse P, Arbuck SG, Eisenhauer EA et al. J Natl Cancer Inst 2000, 92:205-216, New guidelines to evaluate the response to treatment in solid tumors.
2. Rustin GJ, Quinn M, Thigpen T et al. J Natl Cancer Inst 2004, 96:487-488, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.
3. Vergote I, Rustin GJ, Eisenhauer EA et al. J Natl Cancer Inst 2000, 92:1534-1535, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.
4. Taylor PT, Haverstick D. J Natl Cancer Inst 2005, 97:151, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].
5. Rustin GJS. J Natl Cancer Inst 2005, 97:152, Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer].