

## Should CA-125 Response Criteria Be Preferred to Response Evaluation Criteria in Solid Tumors (RECIST) for Prognostication During Second-Line Chemotherapy of Ovarian Carcinoma?

Bo Gronlund, Claus Høgdall, Jørgen Hilden, Svend A. Engelholm, Estrid V.S. Høgdall, and Heine H. Hansen

From the Departments of Oncology and Gynecology, Rigshospitalet, Copenhagen University Hospital; Department of Biostatistics, University of Copenhagen; the Department of Clinical Biochemistry, Statens Serum Institute; and Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.

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Address reprint requests to Bo Gronlund, MD, Department of Oncology 5073, Rigshospitalet, DK-2100 Copenhagen, Denmark; e-mail: bo.gronlund@dadlnet.dk.

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### A B S T R A C T

#### Purpose

The aim of the study was to compare the prognostic value of a response by the Gynecologic Cancer Intergroup (GCI) Cancer Antigen (CA) -125 response criteria and the Response Evaluation Criteria in Solid Tumors (RECIST) on survival in patients with ovarian carcinoma receiving second-line chemotherapy.

#### Patients and Methods

From a single-institution registry of 527 consecutive patients with primary ovarian carcinoma, 131 records satisfied the inclusion criteria: ovarian carcinoma of International Federation of Gynecology and Obstetrics stage IC to IV, first-line chemotherapy with paclitaxel and a platinum compound, refractory or recurrent disease, and second-line chemotherapy consisting of topotecan or paclitaxel plus carboplatin. Univariate and multivariate analyses of survival were performed using the landmark method.

#### Results

In patients with measurable disease by RECIST and with assessable disease by the CA-125 criteria ( $n = 68$ ), the CA-125 criteria were 2.6 times better than the RECIST at disclosing survival. In a multivariate Cox analysis with inclusion of nine potential prognostic parameters, CA-125 response (responders *v* nonresponders; hazard ratio, 0.21;  $P < .001$ ) and number of relapse sites (solitary *v* multiple; hazard ratio, 0.47;  $P = .020$ ) were identified as contributory prognostic factors for survival, whereas the parameters of RECIST (responders *v* nonresponders), as well as the remaining variables, had nonsignificant prognostic impact.

#### Conclusion

The GCI CA-125 response criteria are a better prognostic tool than RECIST in second-line treatment with topotecan or paclitaxel plus carboplatin in patients with ovarian carcinoma.

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### INTRODUCTION

Whereas cure is possible in primary epithelial ovarian carcinoma, recurrent disease is generally considered as incurable.<sup>1,2</sup> Patients with recurrent disease are candidates for second-line cytotoxic treatment, and palliation of symptoms and improved survival are the main therapeutic goals. These end points may be difficult to monitor, and

the adjustment of the salvage treatment most often has been guided by intermediate end points, such as response evaluation by imaging-based tumor response criteria, assuming a correlation between a tumor response and longer survival.<sup>3,4</sup> In several phase II studies, a correlation between a cancer antigen (CA) -125 response and a reduction in tumor size was found when monitoring the impact of second-line

chemotherapy in patients with pretreated ovarian carcinoma.<sup>5-7</sup> All these studies included patients treated with first-line regimens other than paclitaxel plus platinum, now internationally regarded as standard first-line chemotherapy,<sup>8</sup> which may change the chemosensitivity of the tumor in the second-line clinical setting. However, it is not clear whether tumor marker–guided response criteria or imaging-based response criteria best reflect the outcome of second-line chemotherapy in terms of survival.<sup>9</sup>

The aim of the study was to compare the prognostic value of a response by the recently introduced Gynecologic Cancer Intergroup (GCIIG) simplified CA-125 response criteria and the Response Evaluation Criteria in Solid Tumors (RECIST) on survival after start of second-line chemotherapy in a well-defined cohort of patients with ovarian carcinoma all pretreated with paclitaxel plus platinum as first-line treatment.

## PATIENTS AND METHODS

### The Registry

Since 1994, when paclitaxel plus platinum was introduced as standard first-line chemotherapy for ovarian carcinoma at the Rigshospitalet, all patients with ovarian tumors have been consecutively registered. The clinical data from patients with recurrent epithelial ovarian carcinoma have been included in a clinical database (Copenhagen Database for Ovarian Carcinoma; The Danish Data Protection Agency No. 2000-41-0126).

First-line chemotherapy consisted of paclitaxel (175 mg/m<sup>2</sup> as a 3-hour infusion) followed by either carboplatin (area under the curve of 5) or cisplatin (75 mg/m<sup>2</sup>) repeated every 3 weeks.<sup>10</sup> Second-line chemotherapy has been standardized as follows: patients classified as platinum-resistant were offered single-drug treatment with topotecan 1.0 mg/m<sup>2</sup> administered intravenously on days 1 through 5 every 21 days.<sup>11</sup> They comprised patients with progression of disease (refractory disease) during first-line treatment, patients with persistent disease after the end of first-line therapy, and patients who responded and subsequently experienced relapse within 6 months after discontinuation of first-line chemotherapy. Patients with a treatment-free interval of more than 6 months after the end of first-line treatment have been considered platinum-sensitive, and they were re-treated with paclitaxel plus carboplatin using a schedule similar to the first-line treatment.<sup>12</sup> Some other patients with refractory, persistent, or recurrent disease were included in various phase II studies of investigational approaches. Other second-line regimens included oral topotecan, topotecan with oral etoposide, topotecan plus doxorubicin, topotecan (1.2 mg/m<sup>2</sup>), ifosfamide, paclitaxel, encapsulated liposomal doxorubicin, oral melphalan, or no further chemotherapy in patients after complete tumor resection in relation to secondary cytoreductive surgery or in patients who refused treatment.

The efficacy of the second-line chemotherapy was routinely assessed by imaging techniques (computed tomography [CT] scan or abdominal and endovaginal ultrasonography) after every two courses of treatment. Senior consultants at the department of radiology performed the ultrasonographies. All patients underwent serum CA-125 measurement before each cycle of second-line

chemotherapy. Duration of treatment depended on the evaluation of response and followed departmental guidelines for standard second-line therapy. In patients declared to have obtained a complete response, chemotherapy was continued for two cycles after a complete response was achieved. In patients with a partial response or stable disease, standard antineoplastic therapy was continued until tumor progression. Patients with progressive disease or unacceptable toxicity were offered several different options, including inclusion in phase II protocols involving various investigational approaches, endocrine therapy, or supportive care.

### Inclusion Criteria

Records were selected from the registry using the following inclusion criteria: epithelial ovarian carcinoma of International Federation of Gynecology and Obstetrics (FIGO) stage IC to IV; first-line chemotherapy with paclitaxel and a platinum compound; refractory, persistent, or recurrent disease diagnosed by imaging methods (CT scans or ultrasonographies); second-line chemotherapy consisting of topotecan or paclitaxel plus carboplatin; and start of second-line chemotherapy before January 1, 2002. Separately analyzed were patients with nonmeasurable disease by the RECIST or with nonassessable disease by the GCIIG CA-125 response criteria. Because of the many different second-line regimens and the low patient number ( $n < 25$ ) in the treatment groups other than topotecan or paclitaxel plus carboplatin, these patients were not included in the present analysis. The start of second-line chemotherapy before January 1, 2002, was chosen to ensure proper follow-up time for the survival analyses.

### RECIST

The RECIST were used to verify response.<sup>13</sup> Briefly, a response is defined as at least a 30% decrease in the baseline sum longest diameter. A nonresponse is defined as less than a 30% decrease or an increase in the baseline sum longest diameter. Patients having solid tumors assessed by CT scan ( $> 10$  mm) or by ultrasonography ( $> 20$  mm) were defined as having measurable disease. Nonmeasurable disease was defined as lesions measuring less than 10 mm by CT scan or less than 20 mm by ultrasonography. Nonmeasurable disease included cystic lesions and ascites and also patients in whom the response assessment was performed by different imaging techniques.

### GCIIG CA-125 Response Criteria

In all patients, serum levels of CA-125 were determined using a CA-125 enzyme immunoassay (Abbott CA125 EIA; Abbott Laboratories, Chicago, IL). The within-assay coefficient of variation was 6.6% ( $n = 60$ ), whereas the between-assay coefficient of variation was 6.2% ( $n = 10$ ) at a control sample of 30 units/mL. All serum samples were analyzed at the same laboratory (The Statens Serum Institute).

The CA-125 alterations were evaluated by using the recently introduced GCIIG CA-125 response criteria.<sup>14</sup> Briefly, two pretreatment samples at least twice ( $\geq 70$  units/mL) the upper cutoff of normal ( $> 35$  units/mL) and at least two additional samples after the start of treatment are required to have assessable disease. A response has occurred if there is at least a 50% decrease in CA-125 levels that is confirmed by the fourth sample.

### Survival

The prognostic impact of a RECIST response (responders  $\nu$  nonresponders) and a CA-125 response (responders  $\nu$  nonresponders) on survival were retrospectively analyzed by the landmark method.<sup>15,16</sup> Briefly, the method consists of ignoring

responses that occur after an arbitrary landmark day. Patients are followed from that time point onwards, and their survival is related to the response classification as assessed at the landmark. In this study, the landmark was arbitrarily defined as the day of the first clinical evaluation after four cycles of second-line chemotherapy. The response status by the RECIST was thus examined by comparing the pretreatment tumor burden at the start of second-line chemotherapy (cycle No. 1) to the tumor burden after cycle No. 4. The first response evaluation after cycle No. 4 was the one performed just before cycle No. 5. The exact date of the evaluation was used for landmark, and it fell approximately 12 weeks after the start of second-line chemotherapy. Similarly, the CA-125 response on the landmark date was registered by comparing the pretreatment CA-125 levels with the CA-125 level on this date. The following patient categories were not used in the survival analyses: patients in whom the second-line treatment was discontinued for any reason before full four cycles of chemotherapy and with a survival longer than 12 weeks after start of second-line chemotherapy, or patients who died before the landmark time. Survival was calculated from the landmark date to death or the date of analysis (June 1, 2003).

### Statistical Methods

Both the RECIST and the CA-125 classifications are binary (responders v nonresponders) in what follows. Using the Kaplan-Meier product-limit method, survival curves as function of response were constructed for the RECIST and the CA-125 response criteria and compared using the log-rank test. Analogous survival analyses were performed for other potential prognostic factors: FIGO stage, histology, residual disease after staging operation, initial performance status, response to first-line treatment, treatment-free interval (TFI) from the end of first-line chemotherapy to the first day of second-line chemotherapy, age, performance status, and number of relapse sites at time of second-line treatment. All factors were analyzed as categoric variables. To evaluate the ability of the RECIST and the CA-125 criteria to predict survival, the parameters of RECIST response and CA-125 response were analyzed using Cox regression. The following Cox models were analyzed: (A) with the parameters of RECIST response and CA-125 response being taken into account separately, (B) with both of the parameters of RECIST response and CA-125 response included as survival predictors, (C) with inclusion of RECIST response and CA-125 response and other potential prognostic factors, and (D) with inclusion of RECIST response and CA-125 response and other potential prognostic factors in patient subgroups (monotherapy and combination second-line chemotherapy, respectively). The survival of the patient subgroups assessable by none or only one of the two response classifications is illustrated using Kaplan-Meier plots. The differences in survival between the subgroups were tested two by two using the log-rank test. SPSS statistical software (version 10.0; SPSS Inc, Chicago, IL) was used.

## RESULTS

### Study Population

In the period from August 1994 to July 2001, 527 consecutive patients with primary ovarian carcinoma received first-line treatment with paclitaxel plus platinum after an initial staging operation. Of these, a total of 131 patients fulfilled the inclusion criteria. A further 127 pa-

tients had refractory/persistent/recurrent disease treated with second-line regimens other than topotecan or carboplatin plus paclitaxel. The remaining 269 patients in the cohort had primary ovarian cancer without relapse. Forty-nine of the 131 patients had nonmeasurable disease by RECIST ( $n = 17$ ), nonassessable disease by GCIG CA-125 criteria ( $n = 20$ ), or simultaneous nonmeasurable disease and nonassessable disease ( $n = 12$ ). Another 13 patients were removed from the survival analyses because they died before the landmark evaluation, in addition to one patient who received fewer than four cycles of second-line chemotherapy, thus leaving 68 patients for the direct comparison of the two prognostic classifications.

The characteristics of the patients ( $n = 68$ ) are listed in Table 1. The patients received a median of seven cycles (range, three to 14 cycles) of paclitaxel plus platinum as first-line treatment. Median TFI was 9.4 months (range, 0.9 to 51.3 months). The median patient age at the start of

**Table 1.** Patient Characteristics

Characteristic	No. of Patients	%
Total	68	100
FIGO stage		
I-II	3	4
III	49	72
IV	16	24
Histology		
Serous	39	57
Mucinous	2	3
Other	27	40
Residual disease after staging operation, cm		
$\leq 1$	19	28
$> 1$	49	72
Initial performance status		
0	50	74
1-2	18	26
Response to first-line treatment		
Responders	54	79
Nonresponders	5	7
NM or NA	9	13
Treatment-free interval, months		
$\leq 6$	21	31
6-12	22	32
$> 12$	25	37
No. of relapse sites		
Solitary	18	26
Multiple	50	74
Performance status at time of second-line chemotherapy		
0	46	68
1-2	22	32
Age at time of second-line chemotherapy, years		
$\leq 65$	41	60
$> 65$	27	40

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; NM, Nonmeasurable; NA, Nonassessable.

second-line chemotherapy was 60.5 years (range, 34.8 to 77.2 years). Second-line chemotherapy included topotecan ( $n = 31$ ) or paclitaxel plus carboplatin ( $n = 37$ ), and a median of seven second-line cycles (range, four to 16 cycles) was provided for salvage treatment. The latest day of start of second-line chemotherapy was December 17, 2001.

The response rates by the RECIST and the GCIG CA-125 criteria after four cycles of second-line chemotherapy (landmark time) are listed in Table 2. The response criteria were concordant in 81% (95% CI, 70% to 89%; 55 of 68 patients) and discordant in 19% (95% CI, 11% to 31%; 13 of 68 patients) of patients. Of the 34 patients categorized as non-responders by RECIST at landmark time, five patients (15%) with stable disease obtained a subsequent partial response (late response) after further second-line treatment.

### Survival

At the time of analysis, four patients (6%) are alive without demonstrable disease, and six patients (9%) are alive with disease, whereas 58 patients (85%) have died with disease. All patients died from cancer-related disease. No patients were lost to follow-up.

In a univariate analysis, survival after the landmark time was significantly longer in patients with a response according to RECIST compared with nonresponders ( $P = .035$ ). Median survival (50% survival fraction) of responders and nonresponders was 20.2 months (range, 0.8 to 39.3 months) and 9.2 months (range, 1.7 to 37.0 months), respectively (Fig 1). With the GCIG CA-125 criteria, the results were analogous. The survival of responders according to the CA-125 response criteria was significantly longer compared with that of nonresponders ( $P < .0001$ ). Median survival of responders and nonresponders was 20.4 months (range, 1.2 to 39.3 months) and 5.3 months (range, 0.8 to 23.3 months), respectively (Fig 2).

Survival from the landmark time was also significantly different for the parameters of TFI  $\leq 6$  versus more than 6 months ( $P = .0002$ ) and TFI  $\leq 12$  versus more than 12 months ( $P = .012$ ). No significant univariate differences in survival were found for the following factors: FIGO stage (I + II  $\nu$  II I + IV;  $P = .19$ ), histology (serous  $\nu$  nonserous;

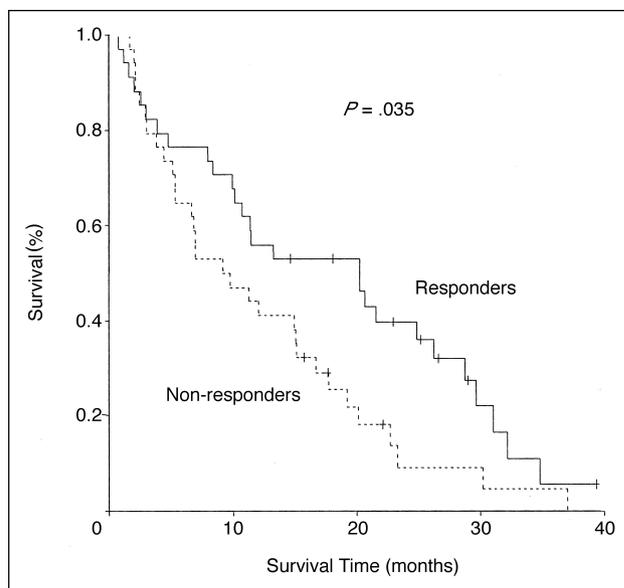


Fig 1. Survival according to Response Evaluation Criteria in Solid Tumors.

$P = .47$ ), residual disease after initial operation ( $\leq 1$  cm  $\nu$   $> 1$  cm;  $P = .15$ ), initial performance status (0  $\nu$  1 to 2;  $P = .19$ ), response to first-line treatment (response  $\nu$  no response;  $P = .78$ ); age at time of second-line chemotherapy ( $\leq 65$  years  $\nu$   $> 65$  years;  $P = .63$ ), number of relapse sites (solitary  $\nu$  multiple;  $P = .07$ ), and performance status at time of second-line chemotherapy (0  $\nu$  1 to 2;  $P = .07$ ).

The results from the Cox analyses are listed in Table 3. The GCIG CA-125 response criteria are thus two to three times ( $[1/0.23]/[1/0.57]$ ) better than the RECIST at disclosing

**Table 2.** Response by the RECIST and the GCIG CA-125 Tumor Response Criteria After Four Cycles of Second-Line Chemotherapy (landmark time)

CA-125 Criteria	RECIST					
	Responders		Nonresponders		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Responders	31	46	10	15	41	60
Nonresponders	3	4	24	35	27	40
Total	34	50	34	50	68	100

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; GCIG, Gynecologic Cancer Intergroup; CA, Cancer Antigen.

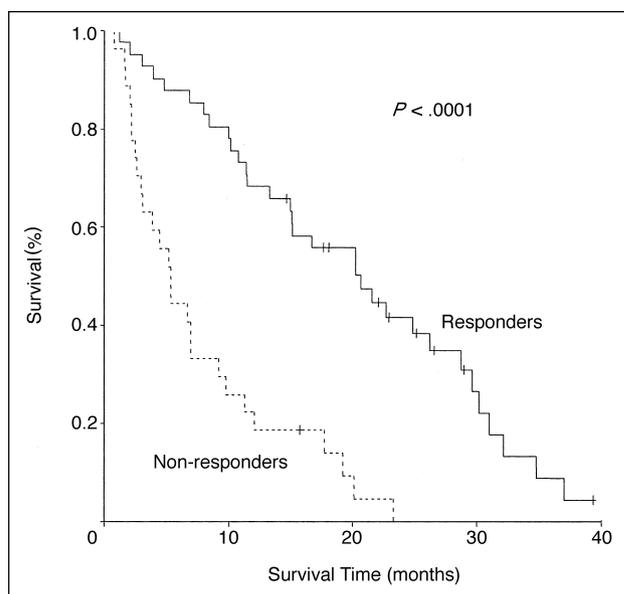


Fig 2. Survival according to Gynecologic Cancer Intergroup Cancer Antigen (CA)-125 response criteria.

**Table 3.** Survival: Results of Cox Analyses

Analysis	Variable	Hazard Ratio	95% CI	P
Cox analysis No. 1	RECIST response	0.57	0.33 to 0.97	.037
Cox analysis No. 2	CA-125 response	0.23	0.13 to 0.42	< .001
Cox analysis No. 3*	RECIST response	1.66	0.70 to 3.92	.25
	CA-125 response	0.16	0.06 to 0.39	< .001
Cox analysis No. 4†	RECIST response	—	—	—
	CA-125 response	0.21	0.11 to 0.38	< .001
	No. of relapse sites, solitary v multiple	0.47	0.25 to 0.88	.020
Cox analysis No. 5‡	RECIST response	—	—	—
	CA-125 response	0.47	0.29 to 0.76	.002
	No. of relapse sites, solitary v multiple	0.23	0.07 to 0.76	.015
	Age, ≤ 65 years v > 65 years	0.39	0.16 to 0.92	.033
Cox analysis No. 6§	RECIST response	—	—	—
	CA-125 response	0.55	0.33 to 0.91	.022

NOTE. RECIST and Gynecologic Cancer InterGroup CA-125 response: responders v nonresponders.

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CA, cancer antigen.

\*Both response classifications are included in the regression model.

†No independent prognostic value was found for any of the following covariates: International Federation of Gynecology and Obstetrics stage, histology, residual disease after staging operation, initial performance status, response to first-line treatment, treatment-free interval (6 months), age, and performance status at time of second-line treatment.

‡Patients treated with topotecan (n = 31).

§Patients treated with paclitaxel plus carboplatin (n = 37).

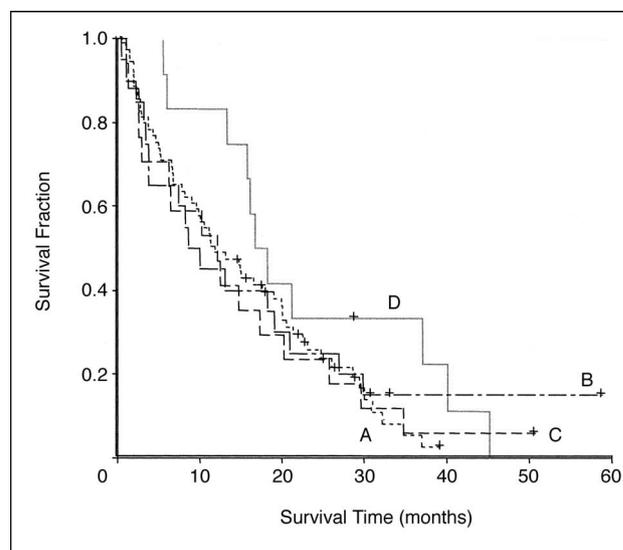
survival (Cox analyses No. 1 and 2). A more refined estimate takes the responder-to-nonresponder ratio into account (Table 2) and forms the ratio of the two prognostic efficacies, as follows:  $[\ln 0.23\sqrt{(41/68)(27/68)} / \ln 0.57\sqrt{(34/68)(34/68)}] = 2.6/1$ . In a multivariate Cox analysis (Cox analysis No. 4) with inclusion of potential prognostic parameters, CA-125 response (hazard ratio, 0.21;  $P < .001$ ) and number of relapse sites (solitary v multiple; hazard ratio, 0.47;  $P = .020$ ) were identified as contributory prognostic factors for survival, whereas the parameters of RECIST, as well as the remaining variables, had nonsignificant prognostic impact (Table 3). A multivariate Cox analysis with inclusion of TFI 12 months instead of TFI 6 months yielded similar results. The advantage of the CA-125 criteria compared with the RECIST in prognosticating survival was also present in the subgroups of patients (n = 31) treated with monotherapy (Cox analysis No. 5) and in patients (n = 37) treated with combination therapy (Cox analysis no. 6).

The survival of the different patient subgroups assessable by none, one, or both of the two response classifications are illustrated in Figure 3. The median survival of patient groups A, B, C, and D were 11.7 months (range, 0.8 to 39.3 months), 9.3 months (range, 0.5 to 58.8 months), 12.1 months (range, 1.1 to 50.7 months), and 17.5 months (range, 5.5 to 45.2 months), respectively. There was no difference in survival between the patient categories A, B, C, and D (log-rank tests:  $P > .05$ ).

## DISCUSSION

In second-line treatment of epithelial ovarian cancer, CA-125–based tumor response criteria and imaging-based re-

sponse criteria have been compared in several studies, finding a concordance between an imaging-based tumor response and a response by CA-125 criteria ranging from 30% to 85%.<sup>5-7,17,18</sup> This is the first study that compares the prognostic impact of a response by different tumor response criteria on survival in patients with recurrent or refractory ovarian tumors, demonstrating that response assessment by GCIG CA-125 criteria is superior to RECIST in



**Fig 3.** Survival of patient subgroups (A through D) assessable by none, one, or both of the two response classifications (Response Evaluation in Solid Tumors [RECIST] and Gynecologic Cancer InterGroup Cancer Antigen (CA)-125 criteria). (A) RECIST, yes, and CA-125, yes (n = 68); (B) RECIST, yes, and CA-125, no (n = 20); (C) RECIST, no, and CA-125, yes (n = 17); (D) RECIST, no, and CA-125, no (n = 12).

predicting survival in this group of patients. The parameter of CA-125 response after four cycles of second-line chemotherapy was found to possess an independent impact as a prognostic factor for survival, whereas the parameter of RECIST response had no demonstrable independent influence on survival, neither in a bivariate nor in a multivariate analysis of prognostic factors. Hence the inclusion of nine potential prognostic parameters to adjust for the influence of confounding factors did not change the result of GCIIG CA-125 response as holding independent prognostic information on survival. In a round-shaped tumor, a 30% reduction in the diameter (to obtain a response by RECIST) equals a 50% decrease in the area of the tumor.<sup>13,19</sup> Halving of baseline CA-125 levels is thus a better predictor of survival than a halving of the tumor surface area determined by conventional imaging methods.

These findings are in agreement with the biology of the disease. Recurrent ovarian carcinoma often spreads to peritoneal surfaces, forming multiple peritoneal implants that cannot readily be detected by conventional imaging techniques (CT scans or ultrasonography).<sup>20</sup> It can be questioned how well the indicator lesions for tumor measurement reflect the overall tumor load. A chemotherapy-induced stabilization of the indicator lesions may be registered simultaneously with a considerable regression of diffuse carcinosis that is not measurable by RECIST and is therefore not included in the overall evaluation of the RECIST tumor response. CA-125, a glycoprotein expressed on the surface of ovarian cancer cells, may thus better reflect the total tumor load.

However, it is uncertain whether a CA-125 response predicts the efficacy of chemotherapy or merely reflects the course of the disease, regardless of treatment given. In fact, it is unknown how the CA-125 levels would evolve if the chemotherapy had been discontinued. Ovarian cancer relapses are heterogeneous tumors with different expression of CA-125 in the different tumor clones. Agents that induce a reduction in CA-125 levels do not necessarily reduce the overall tumor growth. The alterations in CA-125 levels caused by the administration of an agent depends on several factors, such as the tumor clone mix, the agent's affinity for tumor cells expressing CA-125, and the agent's interference with CA-125 metabolism. The changes in CA-125 levels after the administration of a specific agent may be different using another agent. However, the advantage of the CA-125 criteria to RECIST in prognosticating survival was present both in patients receiving topotecan and in patients receiving paclitaxel-carboplatin (Table 3).

The difference in the impact on survival between the RECIST and the CA-125 criteria may be further explored by an examination of the discordant cases. At the landmark time, 19% of patients had discordant response status (Table 2). It may be that a RECIST response occurred later than the landmark time, thus including a landmark time-related

selection bias in the survival analysis. However, late RECIST response was observed in only five (15%) of 34 patients. Interestingly, all the five patients had stable disease (RECIST, nonresponders) at time of landmark, and anti-neoplastic therapy was continued in these patients until tumor progression according to departmental guidelines. Therefore, there was not any potential danger of inappropriately having changed therapy in these patients.

A central question is whether the findings have any implication for how to monitor second-line chemotherapy in daily clinical practice. Prolongation of survival is a major goal among other goals, which also include the palliation of symptoms and increasing the general quality of life. As the CA-125 criteria better prognosticate survival than the RECIST, the study may indicate that tumor marker-guided response criteria should be preferred to imaging-based response criteria in the monitoring of salvage chemotherapy. However, a number of caveats should be voiced in this regard.

The advantage of the CA-125 criteria compared with the RECIST is manifest only in patients assessable by both criteria. A total of 32 patients had nonassessable disease by CA-125 criteria, but 20 of these had measurable disease by RECIST, and in such patients, the treatment should still be monitored by imaging-based methods. Twelve patients had nonassessable and nonmeasurable disease, and in such cases, the monitoring of second-line therapy is quite difficult. This emphasizes the necessity of evaluation of other potentially usable tumor markers such as tetranectin<sup>21</sup> or cancer-associated serum antigen<sup>22</sup> in patients with nonmeasurable and CA-125 nonassessable disease.

The findings in the present study are valid only for patients treated with either topotecan or paclitaxel plus carboplatin (Table 3). Other agents or combinations of agents may act differently, and other findings of the impact of CA-125 criteria and RECIST may be observed. The impact of the CA-125 criteria and the RECIST in prognosticating survival should thus be examined for every single agent or combinations. Noteworthy, 127 patients receiving second-line regimens other than topotecan or paclitaxel plus carboplatin in the cohort were not included in this analysis, which may present a potential selection bias. However, the inclusion of these groups would add to the heterogeneity of the study population and potentially obscure and confound the analyses.

Imaging-based tumor response criteria, such as the RECIST, are based on visualization of the shrinkage and disappearance of the tumor. This gives rise to some methodologic problems because imaging-based response criteria can be confounded by inaccuracies in the use of the radiographic techniques.<sup>23</sup> In the RECIST guidelines, the ultrasound technique is generally discouraged for tumor response evaluation because of the interference from bowel gas in the measurement of para-aortic lesions and

subjectivity in the interpretation of tumor size.<sup>13</sup> In ovarian carcinoma, most recurrences are located in the pelvic region, where the vaginal ultrasound technique is comparable to CT scans.<sup>24</sup> Furthermore, many pelvic relapses are located around the top of the vagina, which may act as an anatomic landmark for reproducible measurements.

The relationship between response and survival contains a number of potential biases and has been intensively discussed in the oncologic literature.<sup>15,16,25-27</sup> A bias that may contribute to the long survival in patients with a response is the guarantee-time effect. Patients whose records refer them to a definite response category must have lived long enough for the change in their condition to occur and be formally recorded. To minimize the effect of this bias, we used the landmark method in which the patients were followed forward in time from the postfourth cycle evaluation, and survival of the response categories from this arbitrarily defined landmark could be compared without bias, according to Buyse and Piedbois.<sup>16</sup> In fact, by using this method, the time origin is shifted to the right, so that response can be handled as any other prognostic factor known at the origin of the survival assessment. The major disadvantage of the landmark method is that the results and conclusions depend on the selection of the landmark time. If the landmark interval chosen is too short, many responses are ignored; if it is too long, many early deaths are ignored. In this study,

the selected landmark was the time of the clinical evaluation after four cycles of second-line chemotherapy, and by that, 14 patients (17%) were discarded from the survival analyses because of having received fewer than four cycles or because of early death. If, alternatively, the evaluation after six cycles of chemotherapy had been chosen for landmark, even more cases would have been discarded.

In conclusion, a response by GCIG CA-125 criteria to second-line chemotherapy with topotecan or paclitaxel plus carboplatin is associated with a survival gain also after correction for prognostic factors and elimination of the guarantee-time effect. This retrospective analysis indicates that CA-125 response criteria are a better prognostic tool than the RECIST in the second-line treatment of ovarian carcinoma pretreated with paclitaxel plus platinum and are presumably also preferable as a therapeutic monitoring tool in salvage treatment. The question of monitoring, however, should be elucidated in a randomized trial comparing the CA-125 criteria and the RECIST in the monitoring of salvage chemotherapy using survival and quality of life as outcome parameters, and preferably, it should include agents other than topotecan or paclitaxel plus carboplatin.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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