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Duration of Second or Greater Complete Clinical Remission In Ovarian Cancer: Exploring Potential Endpoints for Clinical Trials

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Abstract

Purpose—To explore benchmarks for future consolidation strategies, we evaluated a strictly defined (normal CA-125 and normal CT) second-complete-remission (CR) ovarian cancer population for 1) the median progression-free survival (PFS), 2) the frequency with which second remission exceeds first, and 3) the proportion of patients in remission at given time points.

Methods—Retrospective sampling was carried out at Memorial Sloan-Kettering (10/1993–12/2000) and the Royal Marsden Hospital (1/1995–4/2003) for the following: histological confirmation and elevated CA-125 at diagnosis; primary surgery; first and second-line platinum-based chemotherapy with CR; and no maintenance therapy.

Results—In 35 patients: 1) the duration of first PFS was 17.8 months (95 % CI, 13.2-24.5 mos); and second PFS was 10.8 months (95% CI, 9.6-12.2 mos); 2) the number of patients with second response longer than first was 3/35 (9%); 3) the proportion of patients remaining in second complete remission is 100% (3 mos), 100% (6 mos), 83% (9 mos), 34% (12 mos), 23% (15 mos) and 8.6% (18 mos), respectively.

Conclusion—1) The median PFS from second complete remission is short. 2) A second response is rarely longer than the first even in this second CR population. 3) The number of patients with a second response longer than the first, or the proportion of patients remaining in complete remission at given time points could be evaluated as an outcome measure in future studies.

Keywords

Ovarian cancer; remission duration; consolidation trials

Introduction

The median overall survival for all patients with advanced ovarian cancer has improved from approximately 1 year in 1975 to in excess of 3 years in 2006. For the subset having optimally debulked disease and treatment with taxane- and platinum-based combination chemotherapy,

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it now exceeds 5 years.[3,4] For the majority of patients, however, the disease course is one of remission and relapse requiring intermittent retreatment.[5-7] Opportunities to improve both overall survival and quality of life would include more effective primary treatment, or the use of effective maintenance or consolidation strategies for patients in remission. [8]

The majority of consolidation and maintenance approaches have been investigated in patients in first clinical remission where the duration of progression-free survival (PFS) and overall survival are well characterized. [4,9,10] Since ovarian cancer patients can respond to second-line therapy, it is very attractive to investigate consolidation approaches for these patients. [11] Effective strategies are needed to prevent or delay relapse, which occurs in nearly all such patients, and the generally shorter time of second or greater remission would allow the rapid assessment of efficacy in clinical trials.

The duration of response to second-line therapy has been poorly characterized. While the PFS is generally reported to be 5.3-12 months if one surveys randomized trials for recurrent platinum-sensitive disease, few studies separately report the time of failure for patients in a second complete clinical remission, [12-14] and this PFS range includes patients with complete response to second-line therapy, as well as those with partial responses and often stable disease. It has been suggested that patients with second-line partial responses and stable disease have a similar time to progression, [15] but the characteristics of relapse from a complete response are not well described.

Recently, a retrospective review of 176 patients evaluated the duration of second response compared with first response and showed that only 4 of 121 assessable responses (3%) were of longer duration than the primary response in a given individual. Second *complete* clinical responses were not separately reported, and responses were defined as either radiographic improvement or CA-125 decline.[11] This study raised the important issue of considering patients as their own control to investigate clinical trial strategies. As an example, a novel treatment that resulted in a predetermined proportion of patients having a second remission of longer duration than the first would be particularly noteworthy.

There is currently great interest in evaluating second-remission consolidation strategies in patients who return to a second *complete* clinical remission, which would be most strictly defined as having a normal CT scan and CA-125 level ≤35 U/ml. In this retrospective study, we therefore sought to apply strict criteria for patient selection and definition of complete response (requiring a return to normal CA-125 and normal CT imaging) and to determine 1) the median progression-free interval, 2) how frequently a second complete response is longer than a first complete response, and 3) the proportion of patients remaining in second remission at defined time points.

Patients and Methods

Retrospective clinical databases at Memorial Sloan- Kettering Cancer Center (MSKCC, New York) and The Royal Marsden Hospital (London, UK) were screened for eligible patients as described below. Investigational review board approval for an anonymous retrospective review was obtained.

The MSKCC population was derived from 2 previously reported patient populations [1,2] selected from all patients treated at Memorial Hospital between October 1993 and December 2000 (Fig. 1). The Royal Marsden Population was derived from all patients treated at the Royal Marsden Hospital between January 1995 and April 2003 (Fig. 2).

All patients had histological confirmation of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, and elevated CA125 at diagnosis. All patients had surgery

including bilateral salpingo-oophorectomy, hysterectomy, omentectomy, and tumour debulking, either as primary treatment or following neoadjuvant chemotherapy. Platinum chemotherapy (either single agent or in combination) was given as part of primary therapy with complete response at the end of treatment. Patients relapsing after primary treatment with evaluable disease, receiving platinum-based second-line chemotherapy, and achieving a second complete response were included. No investigational or maintenance therapy was given in remission. Surgery performed at first relapse was permitted in conjunction with chemotherapy. Patients were observed until second relapse.

Complete responses to first- and second-line therapy were strictly defined by normalization of CA-125 and a normal computed tomography (CT) scan. Disease progression was defined by doubling of the CA-125 above the upper limit of normal (>70 IU/ml), measurable disease on CT, or confirmed disease-related symptoms.

Statistical Considerations

The duration of treatment-free interval (TFI) was measured as the time elapsed from the last dose of chemotherapy until the first dose of the next chemotherapy regimen. The first PFS is measured as the interval from the start of primary therapy to date of first relapse (PFS1). The second PFS is measured as the interval from the start of secondary therapy to the date of the second relapse (PFS2). TFI, PFS1, and PFS2 are reported in months. Median PFS and 95% confidence intervals are estimated using the Kaplan Meier method. Univariate analysis between optimal debulking and PFS was assessed via the log-rank test. All analyses were done using the SAS system, version 9.1 (SAS Institute, Carey, NC).

Results

Based on the selection process described in the methods section, 35 patients were identified for analysis with characteristics as described in Table 1. The median age was 57, ranging from 31-73 years. The majority of patients were stage III or IV (91%), and most had serous or endometrial histology (91%). Three (9%) patients had clear-cell histology. Sixteen (46%) patients had optimal debulking. Thirty-one patients (89%) had primary surgery, and 4 patients (11%) had neoadjuvant chemotherapy (2 RMH + 2 MSKCC). All had a platinum-based primary and second-line regimen that resulted in a return to strictly defined complete clinical remission. The TFI for the entire population was 15.2 months (range, 4.3-72 mos).

Eighty-six percent of patients received 6 or more cycles of primary therapy, and 91% of patients received 6 or more cycles of second-line therapy, as seen in Table 2. The median CA-125 at the end of primary and secondary therapy was respectively 12 U/ml (range, 4-31 U/ml) and 19 U/ml (range, 3-34 U/ml). The duration of the first PFS was 17.8 months (95% CI, 13.2-24.5 mos), and the duration of the second PFS was 10.8 months (95% CI, 9.6-12.2 mos), as seen in Figure 3.

Table 3 shows that primary optimal debulking is associated with a longer duration of the first PFS (24.7 v 14.1 mos, $P = 0.0079$), but the duration of the second PFS is similar regardless of whether primary optimal debulking was achieved (10.9 v 10.6 mos, P = ns).

The number of patients with second PFS longer than first PFS is 3 (9%), with the number of months the second remission is longer for each patient as 0.3 months, 1.7 months, and 6.7 months, respectively, as seen in Table 4. Each of these patients received combination platinum-based primary and second-line therapy. The relationship of PFS1 to PFS2 grouped in categories by the duration of PFS1 is described in Table 5. The 3 patients with PFS2 > PFS1 occurred in patients with duration of PFS1 ranging from 6-20 months. Thus, the duration of first PFS did not predict the longer duration of the second PFS. Figure 4 graphically depicts the duration of

PFS1 and PFS2 for all 35 patients, showing the infrequency of the phenomenon of PFS2 > PFS1.

The proportion of patients remaining in second complete remission is categorized by time in Table 6. The proportion of patients remaining disease-free in PFS2 is 100%, 100%, 83%, 34%, 23% and 8.6% at 3, 6, 9, 12, 15, and 18 months, respectively.

Discussion

There is significant interest in investigating consolidation or maintenance strategies in ovarian cancer for patients in both primary and secondary complete clinical remission. The factors predicting an initial complete response to primary chemotherapy have been well documented and include stage, debulking status, and histology.[16,17] The likelihood of second response following first relapse depends on the TFI and the choice of agent, with most studies having a subset of patients who return to a complete clinical remission. However, the predictive factors and subsequent outcome for this subset are generally not reported separately.[12-14,18,19] Patients in second complete clinical remission are particularly suitable for studies of consolidation strategies, but the lack of agreed-upon endpoints makes pilot trials of this approach difficult to interpret. This study sought to 1) assess the median duration of second complete response using patients selected by strict criteria, 2) characterize the duration of second complete response in relation to the first complete response, and 3) determine the proportion of patients remaining in second complete remission at interval time points. Each of these outcome measures has the potential to be considered for future clinical trial endpoints.

The frequency of achieving a second complete clinical remission varies and directly depends on multiple factors such as the agent employed, whether used singly or in combination, platinum-sensitivity status, and TFI.[12-14,18-20] It also depends on the definition of complete clinical remission. For example, some have proposed that CA-125 is more accurate than WHO or RECIST criteria in ovarian cancer and should preferentially be used; others have defined complete clinical response as having resolution of radiographic evidence of disease (but allowing non-specific abnormalities up to 1 cm), while others have required completely normal CT imaging.[21-24]

First, we have reported the median duration of PFS in this study to be 17.8 months (95% CI 13.2-24.9 mos) following primary therapy. This is similar to the median PFS of 18.5 months recently reported in a trial with 1,308 patients receiving primary paclitaxel and carboplatin treatment in a comparable group.[14] The median TFI in our patient population was 15.2 (range, 4.3-72 mos) representing a moderately platinum-sensitive group. The median duration of PFS2 in our patients of 10.8 months (9.6-12.2 mos) also falls in the range of reported PFS after second-line therapy, but this range comprises data from trials that include both completely (the minority) and partially (the majority) responding patients such as those treated with carboplatin (5.8 ms; 95% CI, 5.2-7.1 mos), gemcitabine with carboplatin (8.6 mos; 95% CI, 7.9-9.7 mos), liposomal doxorubicin with carboplatin (9.4 mos), and paclitaxel with carboplatin (12 mos).[13,14] A retrospective review of patients with a TFI of only 6 months who received a heterogeneous group of treatments for recurrent disease showed a median time to recurrence after second-line therapy of 5 months (range, 1-20 mos). This illustrates the importance of TFI, but this study did not distinguish the proportion of patients with completely responding disease.[25] Clearly the length of the TFI has a major impact on the likelihood of subsequent response (including complete responses), and has been shown to affect PFS following second-line therapy. [26] However, the impact on the duration of second *complete* response was unknown. Our study therefore provides the data suggesting that primary TFI may not be a predictor for longer duration of second complete remission when compared with the first. We also demonstrated, as expected, that optimal debulking is associated with a statistically

longer duration of PFS1 (24.7 v 14.1 mos, $P = 0.0079$), as is well established. [27] However, in this selected patient population, the duration of the second PFS from a second complete response is similar whether or not optimal debulking is achieved (10.9 v 10.6 mos, P = ns). This finding has been documented in other studies with regard to debulking status. [28] This can also be extrapolated from the data of Eisenhauer et al., [29] where the importance of tumor extent in prognosis (post-op residuals varying widely) affected PFS1, but the greater consistency in PFS2 disease (disease volumes at re-tretament) may be more congruent.

Therefore, patients who are able to achieve a second complete response (and represent a selected population) may all behave in a similar fashion irrespective of initial characteristics, but this needs validation in a larger data set.

Second, we also examined the duration of second complete response in comparison to first complete response. A recent report on patients receiving treatment for relapsed ovarian cancer [11] showed that second responses exceed the first response in only 3% of 121 assessable patients, but did not separately report the outcome of the complete responders. Furthermore, the duration of first response could not be used to predict the length of the second response. Our data likewise showed that a longer second response (even using the most stringent criteria to select complete responders) occurred in only 3/35 patients (8%), with differences in duration of 0.3, 1.7, and 6.7 months, respectively. No particular distinguishing characteristics of these patients could be identified. It should be noted that the patient with the 0.3-month difference had a PFS1 of 15.2 months, so achieving a similar duration could be considered clinically meaningful. The numbers are insufficient to determine whether the 3% described by Markman et al., [11] including partial and completely responding patients, differs from the 8% seen in our patients relapsing from complete response. It is reasonable to conclude, however, that the phenomenon of having a second response longer than first is infrequent, even if one confines the analysis to second complete responders.

Third, we have documented the proportion of patients who remain in remission at a given time point (Table 6). When designing a phase II study for second-line treatment where we expect a short median PFS, it may be better to use a binary endpoint such as the 6, 9, 12 month PFS rate. Since this endpoint is binary and observed by the specified time point, traditional phase II design, as is common for tumor-response endpoints, can be utilized. All patients will then be assessed by this fixed time, and this will allow greater uniformity of results across trials.

Clearly the potential for bias exists in our retrospective study. Our numbers are small as a result of the strict eligibility criteria, which aimed to identify the “best” group of patients who would have the potential for showing the longest duration of second complete remission. Our numbers were further diminished by excluding patients that achieved second complete clinical remission by our criteria, but then entered pilot consolidation trials and received investigational therapy. As more clinical trials for recurrent disease include a maintenance or consolidation portion, it is essential that we continue to characterize patient populations such as in this study in order to build the benchmarks necessary to select promising agents from future exploratory studies.

In summary, we have shown that 1) the median PFS from second complete remission is relatively short, and not dissimilar to those reported for patients progressing from partial responses or stable disease; 2) the phenomenon of having a second response longer than first as previously described remains infrequent (8%), even in this ideal second *complete* clinical remission population when retreated with the same or similar agents; 3) the proportion of patients remaining in complete remission at give time points is readily quantified. The latter 2 endpoints should further be explored as future clinical trial outcome measures.

Acknowledgments

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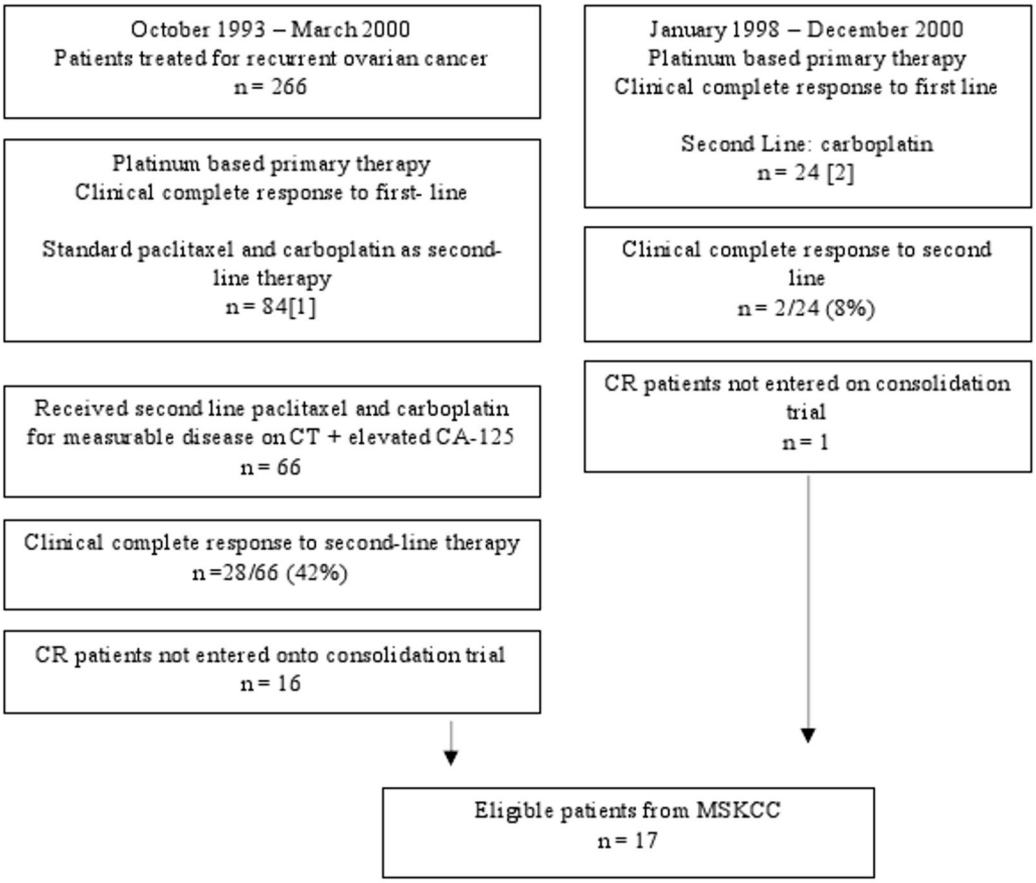

Figure 1. Patient Flow Diagrams: Memorial Sloan-Kettering patient population

CR, complete response; MSKCC, Memorial Sloan-Kettering Cancer Center; TFI, treatment-free interval.

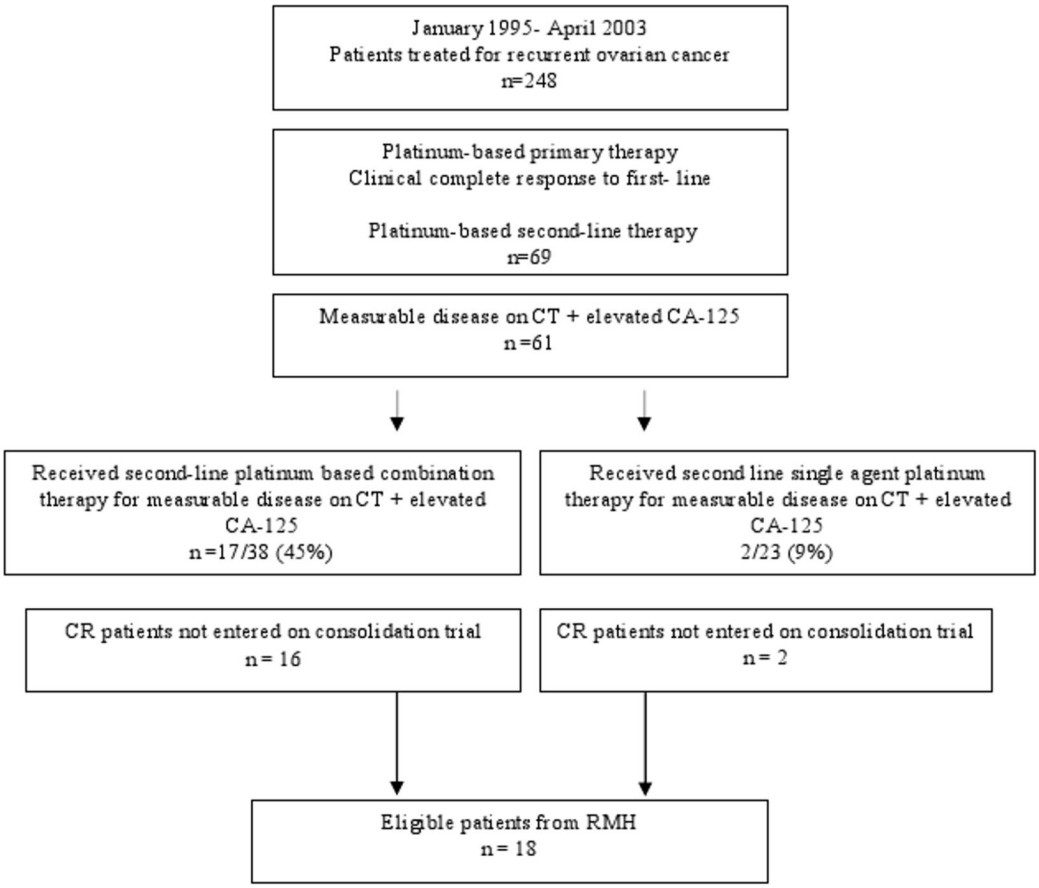

Figure 2. Patient Flow Diagrams: The Royal Marsden patient population

CR, complete response; CT, computed tomography; RMH, Royal Marsden Hospital; TFI, treatment-free interval.

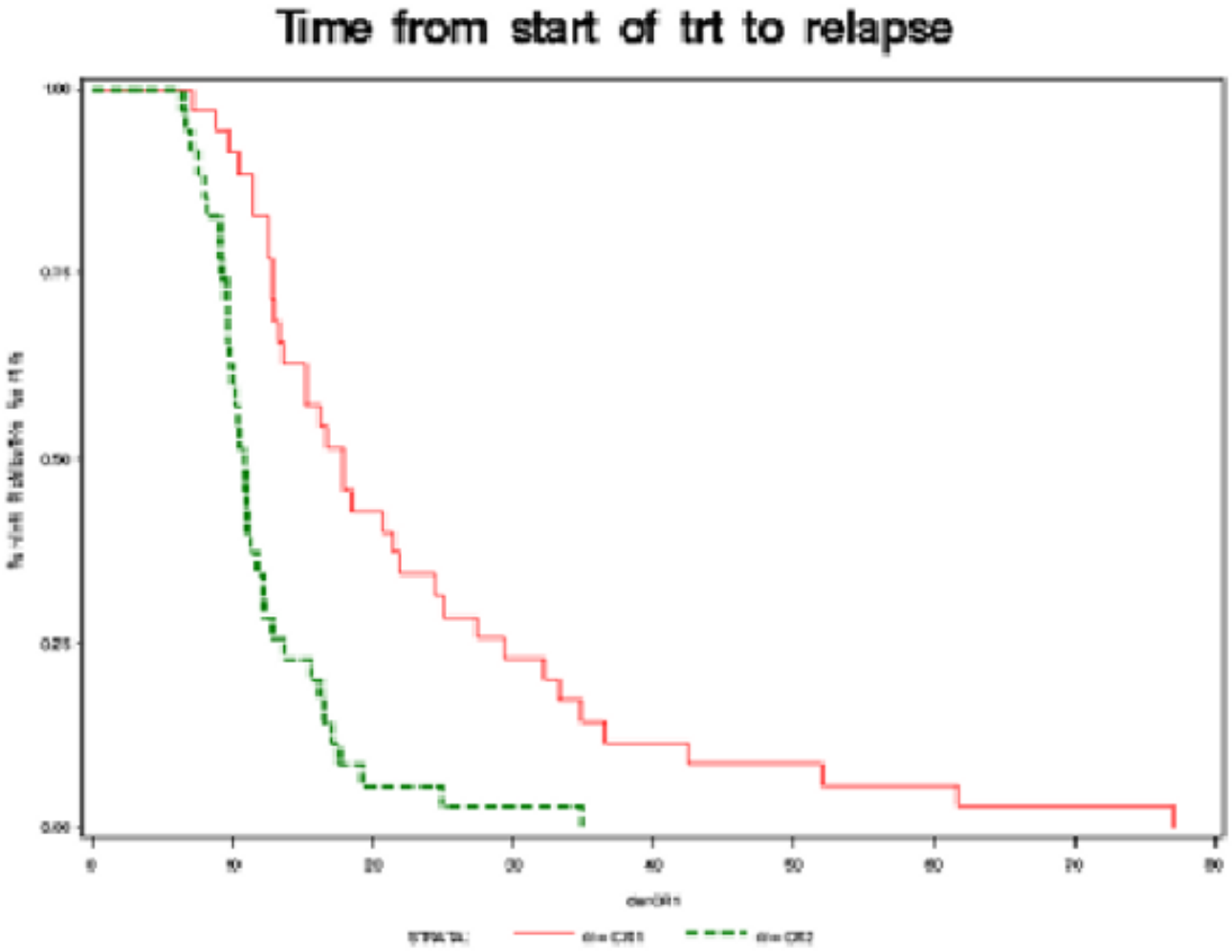

Figure 3. Time from start of therapy to relapse

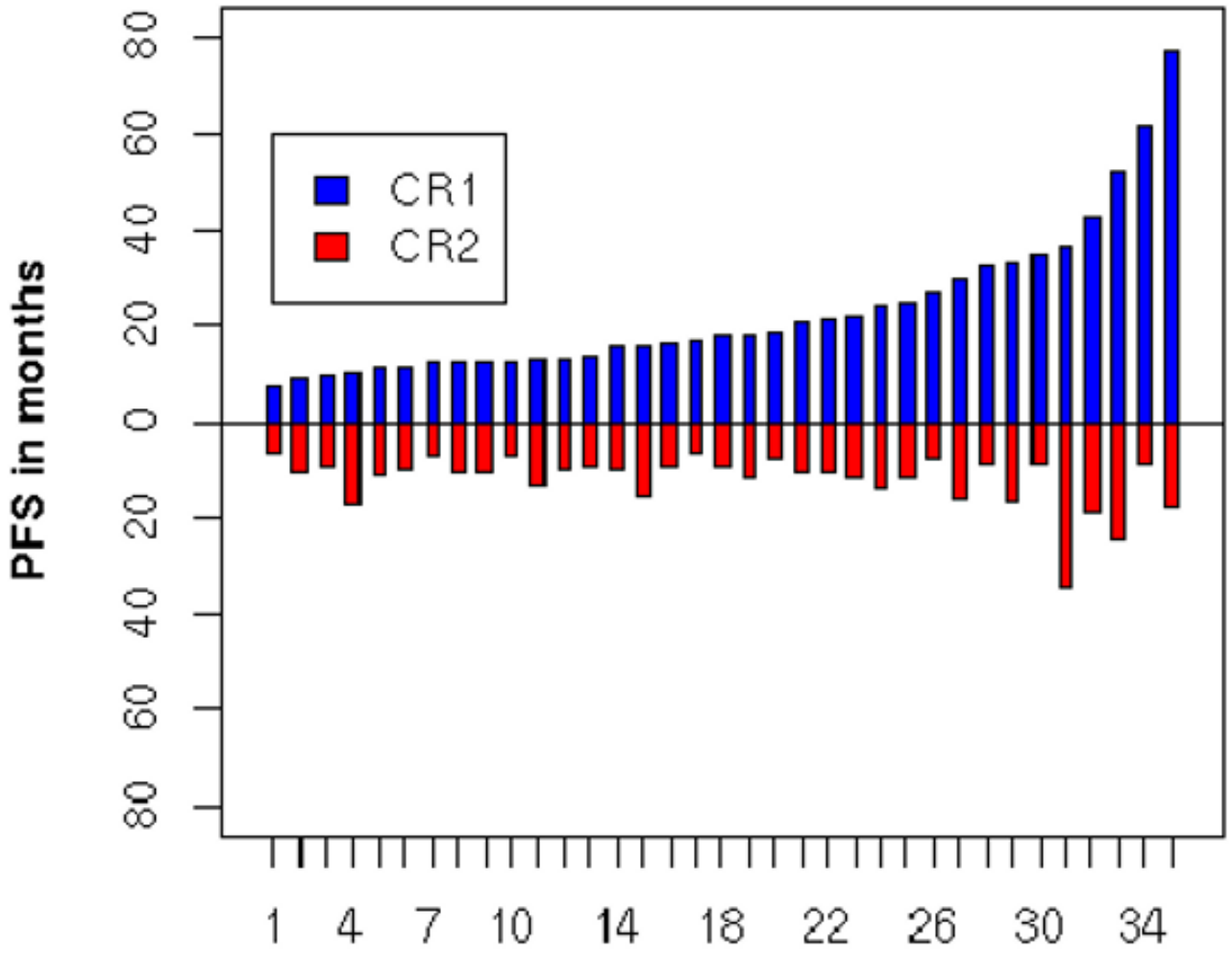

Figure 4. Relationship of PFS1 to PFS2 by patient

Table 1

Patient characteristics

Patient Characteristics (N = 35)	
Median Age, y (range)	**57 (31- 73)**
Stage	
I	2 (6%)
II	1 (3%)
III	24 (69%)
IV	8 (23%)
Histologic Type	
Serous	26 (74%)
Endometrioid	6 (17%)
Clear cell	3 (9%)
Size of Residual at Primary Debulking	
Optimal (≤ 1 cm)	16 (46%)
Suboptimal (> 1 cm)	10 (29%)
Unknown	9 (26%)
Primary Chemotherapy	
Taxane + platinum	22 (63%)
Other platinum containing	13 (37%)
Second-line Chemotherapy	
Taxane + platinum	24 (69%)
Other platinum combination	7 (20%)
Platinum only	4 (11%)

Table 2

Cycles therapy administered, response and response duration

Primary Therapy	**No. Patients (%)**
3 - 5 cycles	5 (14%)
6 cycles	23 (66%)
> 6 cycles	7 (20%)
Second-line therapy	
3-5 cycles	3 (9%)
6 cycles	31 (89%)
> 6 cycles	1 (3%)
Median CA-125 end primary therapy (range)	12 (4-31)
Median CA-125 end second-line therapy (range)	19 (3-34)
Median duration PFS1	17.8 mos, 95% CI (13.2 – 24.5 mos)
Median duration PFS2	10.8 mos, 95% CI (9.6 – 12.2 mos)

PFS1, the interval from the start of primary therapy to date of first relapse; PFS2, the interval from the start of secondary therapy to the date of the second relapse.

Table 3

Relationship of primary debulking status to PFS1 and PFS2

Duration PFS	Optimal	Suboptimal	p
PFS1	24.7 (17.8–34.9)	14.1 (12.5–21.5)	0.0079
PFS2	10.9 (9.3–13.7)	10.6 (9.1–12.2)	.2661

PFS1, the interval from the start of primary therapy to date of first relapse; PFS2, the interval from the start of secondary therapy to the date of the second relapse.

Table 4

Patients with PFS2 > PFS1

Patient no.	Dur PFS1	Dur PFS2	Difference
8	15.2 mos	15.5 mos	0.3 mos
16	8.8 mos	10.5 mos	1.7 mos
17	10.4 mos	17.1 mos	6.7 mos

PFS1, the interval from the start of primary therapy to date of first relapse; PFS2, the interval from the start of secondary therapy to the date of the second relapse.

Table 5

Relationship of PFS1 to PFS2 by category

	PFS2 (mos)						
PFS1 (mos)	**6-9**	**9-12**	**12-15**	**15-20**	**>20**	**Total**	**No. pts PFS2 > PFS1 (dur in mos)**
6-9	1	1	0	0	0	2	1
9-12	0	3	0	1	0	4	1
12-15	2	4	1	0	0	7	0
15-20	2	4	0	1	0	7	1
>20	1	5	3	4	2	15	0

PFS1, the interval from the start of primary therapy to date of first relapse; PFS2, the interval from the start of secondary therapy to the date of the second relapse.

Table 6

Proportion of patients in complete clinical remission at given time points

Time Interval	% in PFS1	% in PFS2
3 months	100%	100%
6 months	100%	100%
9 months	94%	83%
12 months	83%	34%
15 months	63%	23%
18 months	46%	8.6%
21 months	40%	5.8%
24 months	34%	5.8%

PFS1, the interval from the start of primary therapy to date of first relapse; PFS2, the interval from the start of secondary therapy to the date of the second relapse.