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Patient Reported Outcomes of a Randomized, Placebo-Controlled Trial of Bevacizumab in the Front-Line Treatment of Ovarian Cancer: A Gynecologic Oncology Group Study

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Abstract

Purpose—To analyze quality of life (QOL) in a randomized, placebo-controlled phase III trial concluding that the addition of concurrent and maintenance bevacizumab (Arm 3) to carboplatin and paclitaxel prolongs progression-free survival in front-line treatment of advanced ovarian

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Conflicts of Interest

Dr. Monk discloses that he has received a research grant from Genentech to his institution along with serving on the Genentech – Speakers bureaus for which he received an honorarium as a consultant. Additionally, Dr. Robert Burger wishes to disclose that he participates in Advisory Board Meetings for Champions Biotech, Clovis Oncology, Endocyte, Genentech, Boehringer Ingelheim and Marshall-Edwards. Dr. Robert Mannel receives Honoraria for Advisory Board work with Genentech. Finally, Dr. Lari Wenzel serves as a consultant to Roche. There are no further conflicts of interest to disclose.

cancer compared to chemotherapy alone (Arm 1) or chemotherapy with bevacizumab in cycles 2–6 only (Arm 2).

Patients and Methods—The Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI) was used to assess QOL before cycles 1, 4, 7, 13, and 21; and 6 months after completing study therapy. Differences in QOL scores were assessed using a linear mixed model, adjusting for baseline score, and age. The significance level was set at 0.0167 to account for multiple comparisons.

Results—1693 patients were queried. Arm 2 ($p<0.001$) and Arm 3 ($p<0.001$) reported lower QOL scores than those in Arm 1. The treatment differences were observed mainly at cycle 4, when the patients receiving bevacizumab (Arm 2 and Arm 3) reported 2.72 points (98.3% CI: 0.88 ~ 4.57; effect size=0.18) and 2.96 points (98.3% CI: 1.13~4.78; effect size=0.20) lower QOL respectively, than those in Arm 1. The difference in QOL scores between Arm 1 and Arm 3 remained statistically significant up to cycle 7. The percentage of patients who reported abdominal discomfort dropped over time, without significant differences among study arms.

Conclusion—The small QOL difference observed during chemotherapy did not persist during maintenance bevacizumab.

INTRODUCTION

Ovarian cancer is the fourth most common cause of cancer death in women in the United States¹. Improvements in surgical care and delivery of chemotherapy have prolonged overall survival but further progress is needed as the great majority of patients ultimately die from this disease. Angiogenesis is an important factor involved in solid tumor growth and metastasis. Bevacizumab (Avastin®, Roche) is a monoclonal antibody that can inhibit angiogenesis with evidence of efficacy in many solid tumors, including single-agent activity in ovarian cancer^{2,3}.

Two large recently published randomized phase III trials showed that the addition of bevacizumab to standard first-line chemotherapy followed by maintenance bevacizumab improves progression-free survival (PFS) compared to standard chemotherapy^{4,5}. In Gynecologic Oncology Group (GOG) protocol 0218, standard chemotherapy with bevacizumab (Arm 3) followed by maintenance bevacizumab to a maximum of 10 months beyond chemotherapy prolonged progression-free survival (PFS, Hazard Ratio [HR] 0.717; 95% Confidence Interval [CI], 0.625 to 0.824; $p<0.001$) compared to chemotherapy plus placebo (Arm 1) in women with advanced stage epithelial cancer⁴. The impact of antiangiogenic therapy in this setting on survival (OS) is unknown^{4,5}. Other important questions such as dose, treatment duration, cost effectiveness, and whether bevacizumab is best administered at the time of recurrence rather than after initial debulking surgery remain unanswered^{6,7}.

Bevacizumab is associated with toxicities that are occasionally life threatening^{2–6}. In GOG 0218 the rate of hypertension requiring medical therapy was significantly higher in the bevacizumab followed by maintenance bevacizumab group (22.9%) compared to the control group (7.2%)⁴. Though not statistically significant, gastrointestinal-wall disruption requiring medical and/or surgical intervention occurred almost twice as often, 2.6% versus 1.2%,

respectively, and other adverse events such as proteinuria, pain, neutropenia, venous thromboembolism, wound disruption, and central nervous system complications including bleeding and reversible posterior leukoencephalopathy were also more common in bevacizumab treated women. Importantly, no new safety signals were identified in GOG 0218 which enrolled 1873 newly diagnosed stage III or stage IV ovarian cancer patients.

Quality of life (QOL) becomes a major consideration in treatment choice when differences in survival are small or negligible especially when treatments are expensive and toxicities are obvious. In ovarian cancer specifically, patient reported outcomes (PROs) have influenced adoption of new treatments thought to improve clinical outcomes such as PFS⁸⁻¹³.

The primary outcome of GOG 0218 was to determine if the addition of bevacizumab to standard chemotherapy with or without maintenance bevacizumab improved PFS in women with advanced stage ovarian cancer. One of the important secondary study outcomes was to determine the impact of bevacizumab on QOL as measured by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy-Ovary (FACT-O)^{14,15}. With that consideration, the PROs from this study were examined to determine: 1) if anti-vascular endothelial growth factor (VEGF) therapy alters PROs by potentially reducing disease-related symptoms (i.e., improving QOL) more quickly and for more prolonged periods of time than chemotherapy alone; 2) if anti-VEGF (e.g. anti-angiogenesis) therapy alters PROs as a result of treatment-related toxicity not captured through traditional physician-reported measures.

METHODS

Patients

Eligibility criteria included previously untreated, incompletely resected stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer after standard abdominal surgery with maximal debulking effort. A GOG performance status of 0 to 2, no history of clinically significant vascular events, or evidence of intestinal obstruction as well as acceptable end organ function were also required.

Study Design

The study (GOG protocol 0218) was a double-blind, placebo-controlled phase III trial (The redacted protocol is available at NEJM.org)⁴. Each of the three study arms comprised 22 3-week cycles with IV infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve of 6 and paclitaxel at a dose of 175 mg/m² of body-surface area. Arm 1 (Control) included chemotherapy with placebo added in cycles 2 through 22. Arm 2 was chemotherapy with bevacizumab (15 mg/kg) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Arm 3 was chemotherapy with bevacizumab added in cycles 2 through 22. Protocol directed treatment was discontinued at the onset of disease progression, unacceptable toxicity, completion of all 22 cycles, or voluntary withdrawal, whichever came first.

Patient Reported Outcomes

QOL was measured using the FACT-O TOI before cycles 1, 4, 7, 13, and 21; and 6 months after completing protocol-directed therapy^{14,16}(Figure 1). Study subjects completed QOL questionnaires at scheduled assessment time points regardless of disease progression or if protocol directed therapy was stopped secondary to toxicity. This 26-item summary score captures the FACT-G QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7 items), and the Ovarian Cancer Subscale (12 items)¹⁴. By combining these three subscales, we hoped to capture the full range of physical aspects of QOL in advanced ovarian cancer, including pain, fatigue, abdominal symptoms, and functional status. In addition, by combining questions GP4, O1, and O3 into an ovarian cancer abdominal discomfort (AD) subscale, abdominal pain, swelling, and cramps respectively, can be comprehensively assessed to evaluate abdominal symptoms associated with ascites and tumor progression¹⁶. The timing of the QOL assessments was chosen in order to capture data useful in discriminating subtle differences between regimens. This is complicated by the fact that the acute effects of cytotoxic therapy may cause a decrease in QOL. In order to capture early difference in QOL as a result of anti-angiogenesis therapy with bevacizumab, assessment time points during this trial were weighted toward the early part of this study. In addition, since some subjects only complete a few cycles of therapy, it was important to have early assessment points. Finally, in order to avoid the confounding effects of acute chemotherapy related toxicity, questionnaires were completed just before (21 days after the last dose) the next cycle of chemotherapy and with patients' queried on their QOL within the last seven days.

The primary objective of measuring PRO in this trial was to determine if the addition of bevacizumab reduced disease related symptoms (improved QOL) more quickly and for more prolonged periods of time than chemotherapy plus placebo (arm 1). In addition, other objectives of measuring QOL included determining if bevacizumab altered QOL as a result of treatment related toxicity not captured through traditional physician-reported measures.

Statistical Design

The PRO objective in this study was to examine whether the health-related QOL as measured with the FACT-O TOI was different among the three randomized treatment groups.

All patients were included in the analysis regardless of the amount of study treatment they received. The patients were classified by their randomly assigned treatments. Differences in QOL scores between groups were assessed using a linear mixed model, adjusting for baseline score, and age¹⁷. The assessment time points were treated as categorical since they are not equally spaced. The covariance matrix is assumed to be unstructured. To reflect the observed covariance pattern of the TOI scores, the 'empirical' variance was used in estimating the precision of parameter estimates. The interaction between treatment assignments and assessment time points was tested first for differential effects of treatment on TOI scores over time. If the interaction effect was statistically significant, the treatment differences were estimated for each assessment time points. Otherwise the overall treatment effect was estimated by a weighted average of estimates from each time point. To account

for the multiple comparisons of global effects among the three treatment groups, the significant level of hypothesis testing is set at a level of 1.67%¹⁸. The denominator degrees of freedom was approximated as described by Kenward and Roger¹⁹. Treatment effect size was calculated as the ratio of the treatment difference to the baseline standard deviation in the control group (Arm 1). A summary score was based on the FACT-O TOI, with a possible total of 104 points and higher scores indicating better QOL. The sample size was determined by the primary clinical objective (PFS). To avoid any potential biases that could be induced by a subset of study sample, all subjects were included in the QOL component of the study. As such, the study was expected to have approximately 91.4% power to detect a 2.5 unit true difference in mean FACT-O TOI scores between treatment arms. The smallest difference in a domain score of interest perceived by patients as important, and that could lead clinicians to consider a change in the patient's management, was estimated to range between 5 to 8 points using the FACT-O-TOI^{20,21}.

The testing for the effect of bevacizumab on abdominal symptoms was considered exploratory. An examination of the distribution of the AD subscale scores indicated that nearly one-third AD subscale scores are zeros (no abdominal discomfort). Moreover, the nonzero scores were skewed to the right, indicating non-normal distribution of the data. Commonly used methods, such as linear mixed models, assume a normal distribution of data; however, this assumption did not appear appropriate in this situation. Therefore, a mixed effect and mixed distribution model (MEMD) was applied to the AD subscale scores²². This model contained two components. The first component evaluated the probability of scoring a nonzero value and the other modeled the mean of the nonzero scores respectively. The MEMD model incorporated random effects to account for the repeated measures on each subject and the model allowed for correlation between the random effects in the two components.

RESULTS

Between October 2005 and June 2009, 1873 women were enrolled from 336 institutions in the United States, Canada, South Korea, and Japan.

A CONSORT Diagram outlining the enrollment, randomization, and follow-up of the study patients is presented in the publication of the clinical results⁴. Prior to treatment, 1747 patients (93.3%) provided valid QOL assessment and 86.8%, 83.2%, 76.1%, 66.4%, and 59.31% completed valid follow-up assessments prior to cycle 4, cycle 7, cycle 13, cycle 21, and 6 months follow-up respectively. There were no statistically significant differences on the completion rates between the treatment groups. The reasons for missing assessments are summarized in Table 1. The primary reason for missing an assessment at maintenance phase was patient attrition. There were 6% of patients who died prior to cycle 13. The death rates increased to 12% prior to cycle 21 and 21% at 6 months of follow-up. Among the patients who were alive at the time for each QOL assessment, the simple failure to administer the PRO questionnaire was the major reason for noncompliance. However, all subjects and investigators were encouraged to complete all PRO questionnaires on time even if protocol directed therapy was no longer being administered due to progression or toxicity.

There were 87 (5%) patients who did not complete the baseline assessment and 93 (5%) patients who completed only a baseline assessment. These patients were not included in this analysis. Hence, a total of 1693 patients (566 in Arm 1, 554 in Arm 2, and 573 in Arm 3) comprised the sample for the QOL comparisons. Key prognostic factors were balanced among treatment arms (Table 2).

The patients in Arm 2 ($p<0.001$) and Arm 3 ($p<0.001$) reported significantly lower FACT-O TOI scores than those in Arm 1 during the chemotherapy phase of treatment. The treatment differences affecting QOL were observed mainly at cycle 4, when the patients receiving bevacizumab (Arm 2 and Arm 3) reported 2.72 points (98.3% CI: 0.88 ~ 4.57; $p<0.001$; effect size=0.18) and 2.96 points (98.3% CI: 1.13~4.78; $p<0.001$; effect size=0.20) lower QOL according to the FACT-O TOI scores respectively, than those in Arm 1. The difference in FACT-O TOI scores between Arm 1 and Arm 3 remained statistically significant up to cycle 7, which is 2.23 points lower (98.3% CI: 0.33 ~4.14; $p=0.005$; effect size=0.15) in group Arm 3. There were no statistically significant differences between arms 1 and 3 during the maintenance phase. In addition, the scores were not statistically different at any time points between Arms 2 and Arm 3. This is reflected graphically in Figure 2. A similar trend was evident in the subscale analyses, in which the patients in Arm 2 and Arm 3 reported statistically lower functioning than those in Arm 1 (Table 3).

The percentage of patients who reported abdominal discomfort (AD score >0) dropped over time, without significant differences between study arms. The reported abdominal discomfort scores were similar among study arms (Figure 2B and Table 4).

DISCUSSION

Although the incidence of ovarian cancer is less than that of many other solid tumors effecting women, the mortality as well as the associated disease and treatment related morbidity is unacceptably high. Therefore, the need for improvement in therapy is imperative. Initial treatment begins with radical surgery and aggressive courses of chemotherapy; often compromising health-related QOL. In the absence of a clear survival advantage, only those therapies that can improve tumor control without dramatically compromising QOL can be recommended. Indeed, most patients recur after first-line therapy and undergo multiple regimens, all of which may further negatively impacted QOL. As the ongoing search for optimal therapies in both the frontline and recurrent settings continues, attention must be paid towards PRO as well as clinical outcomes.

In addition to examining the extent of treatment benefit, PRO and QOL can aid in decision-making during active treatment and palliative care. In fact, since poor physical well-being as reported at baseline using PRO is independently associated with an increased risk of subsequent death in patients undergoing adjuvant chemotherapy in some trials involving advanced ovarian cancer, implementing supportive care to increase QOL might even improve patient outcomes such as PFS and OS²³.

In the current study, PRO was rigorously analyzed in a placebo controlled randomized phase III trial of bevacizumab in newly diagnosed advanced ovarian cancer. Bevacizumab

compromised QOL, as measured by the FACT-O-TOI, to a mild extent during chemotherapy, but had no prolonged effect after chemotherapy completion. The three point difference between groups during the chemotherapy phase was statistically significant. As the estimated range of a meaningful difference is 5–8 points^{20,21}, it is unclear whether this statistically significant difference is clinically relevant. It may be, or alternatively it may be that the study, powered to support analysis of the PFS endpoint, was overpowered for the QOL endpoint. This QOL difference observed during chemotherapy did not persist during maintenance bevacizumab. Importantly, coming to the clinic every three weeks to receive a placebo during the maintenance phase of the trial may have had a negative impact on QOL. Thus, inherent in the placebo- design of the study, a true comparison of PRO differences between arms 1 and 2 (placebo) compared to arm 3 (bevacizumab) was not possible. Indeed, the current analysis may be an underestimated of the bevacizumab related differences in QOL.

The absence of improved QOL associated with the 3.8 month increase in median PFS and enhanced tumor control is intriguing. This was probably related to the intense surveillance in the study mandating discontinuation of protocol directed therapy when progression was documented by either the Response Evaluation Criteria in Solid Tumors (RECIST) or based upon serum CA-125 alone while patients were asymptomatic^{24,25}. In other words, the addition of bevacizumab could not improve symptoms when disease related symptoms were not present. However, it appears that the increased toxicity associated with adding bevacizumab to chemotherapy had minimal adverse impact upon QOL, and the use of maintenance bevacizumab alone did not have any measurable adverse effect upon QOL.

Although Arm 3 (concurrent and continued bevacizumab) used in the current trial was superior in regards to PFS despite a pre-defined time point for discontinuing bevacizumab in the absence of disease progression, the overall results question whether this should be considered “standard of care” in treating newly diagnosed ovarian cancer. Because patients enrolled onto GOG 0218 were informed of their treatment assignment at the time of disease progression and were likely treated with multiple subsequent regimens including bevacizumab or other anti-angiogenic agents, an analysis of OS on this trial will not be informative²⁶. Finally, no randomized study is planned comparing upfront bevacizumab to bevacizumab at recurrence. Thus, the timing question will most likely never be answered. The final piece of the equation is cost. This will be thoughtfully addressed in an analysis of the current trial integrating the PRO presented here.

In summary, based on the results of GOG 0218 including the PRO data presented here, the use of bevacizumab in advanced ovarian cancer is an acceptable alternative to chemotherapy alone. This mandates a discussion with payers and women with newly diagnosed advanced ovarian cancer about integrating bevacizumab into front-line therapy.

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Figure 1.
Quality of Life (QOL) Assessment Time Points

Mean TOI Score Prior to Disease Progression
by treatment

Figure 2.

Figure 2A. Mean Patient reported Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI) Over Time

Figure 2B. Fraction of patients reporting Abdominal Discomfort (AD>0) and the mean AD Scores reported by those having abdominal discomfort.

Note: The numbers above the bar are patient-reported AD scores by those reporting AD>0.

Table 1

The completion profile of QOL assessments

	Control (Arm 1)	Bevacizumab Initiation (Arm 2)	Bevacizumab Throughout (Arm 3)
No. of Patients Randomized	N=625	625	N=623
Prior to treatment			
Death	1	0	0
Alive	624	625	623
Received and Valid	580 (93%)	570 (91%)	597 (96%)
Noncompliance:			
Illness	3	2	0
Patient Refusal	7	3	2
Administration error	27 (4%)	36 (6%)	18 (3%)
Insufficient responses	3	7	1
Other	4	7	5
Prior to cycle 4			
Death	9	10	14
Alive	616	615	609
Received and Valid	550 (89%)	543 (88%)	532 (87%)
Noncompliance:			
Illness	1	1	0
Patient Refusal	10	10	10
Administration error	37 (6%)	45 (7%)	37 (6%)
Patient Off study	6	5	11
Insufficient responses	1	0	2
Other	11	11	17
Prior to cycle 7			
Death	19	15	24
Alive	606	610	599
Received and Valid	535 (88%)	507 (83%)	516 (86%)
Noncompliance:			
Illness	2	4	4
Patient Refusal	11	10	9
Administration error	38 (6%)	54 (9%)	37 (6%)
Patient Off study	8	11	9
Insufficient responses	0	1	0
Other	12	23	24
Prior to cycle 13			
Death	43	36	35
Alive	582	589	588
Received and Valid	484 (83%)	473 (80%)	469 (80%)

	Control (Arm 1)	Bevacizumab Initiation (Arm 2)	Bevacizumab Throughout (Arm 3)
No. of Patients Randomized	N=625	625	N=623
Noncompliance:			
Illness	3	7	13
Patient Refusal	12	17	13
Administration error	39 (7%)	58 (10%)	52 (9%)
Patient Off study	12	9	13
Insufficient responses	2	1	0
Other	30	24	28
Prior to cycle 21			
Death	74	92	68
Alive	551	533	555
Received and Valid	416 (76%)	395 (74%)	433 (78%)
Noncompliance:			
Illness	14	10	13
Patient Refusal	16	21	14
Administration error	61 (11%)	62 (12%)	49 (9%)
Patient Off study	16	12	4
Insufficient responses	2	0	2
Other	26	33	40
6 Months follow-up			
Death	135	145	112
Alive	490	480	511
Received and Valid	367 (75%)	366 (76%)	378 (74%)
Noncompliance:			
Illness	6	7	6
Patient Refusal	17	15	17
Administration error	62 (13%)	54 (11%)	63 (12%)
Patient Off study	13	10	8
Insufficient responses	0	1	0
Other	25	27	39

Note: Percentages in the brackets are calculated based on the number of patients alive at the scheduled time points.

QOL=Quality of life

Table 2

Characteristics of Patients Included in the Quality of Life Analysis (n=1693)

Characteristic	Arm I	Arm II	Arm III
	Control (n = 566)	Bevacizumab Initiation (n = 554)	Bevacizumab Throughout
Median age, years (range)	60 (25–86)	60 (24–88)	60 (22–89)
GOG performance status, n (%)			
0	284 (50)	287 (52)	289 (50)
1	250 (44)	238 (43)	242 (42)
2	32 (6)	29 (5)	42 (7)
Stage/residual size, n (%)			
III	416 (74)	403 (73)	416 (73)

GOG=Gynecologic Oncology Group

Note: percentages may not total 100% due to rounding or categorization

Table 3

Estimated Least Squares means of QOL scores at each assessment points

	Arm 1		Arm 2		Arm 3	
	Mean	SE	Mean	SE	Mean	SE
Prior to Treatment*	N=556		N=540		N=564	
TOI of FACT-O	68.2	0.64	68.0	0.66	67.4	0.65
Physical Well Being	20.7	0.23	20.5	0.23	20.0	0.24
Functional Well Being	14.8	0.26	14.7	0.27	14.9	0.25
Ovarian Subscale	32.7	0.27	32.8	0.26	32.5	0.26
Prior to cycle 4	N=533		N=524		N=528	
TOI of FACT-O	73.8	0.53	71.1	0.56	70.9	0.54
Physical Well Being	20.7	0.21	19.7	0.21	19.6	0.21
Functional Well Being	17.9	0.22	16.9	0.23	16.7	0.22
Ovarian Subscale	35.3	0.22	34.5	0.23	34.5	0.23
Prior to cycle 7	N=520		n=487		N=512	
TOI of FACT-O	76.0	0.54	74.3	0.56	73.8	0.58
Physical Well Being	21.3	0.20	20.6	0.21	20.4	0.22
Functional Well Being	18.6	0.22	17.9	0.24	17.7	0.23
Ovarian Subscale	36.2	0.22	35.9	0.22	35.6	0.23
Prior to cycle 13	N=471		N=447		N=464	
TOI of FACT-O	80.6	0.62	80.5	0.62	79.9	0.58
Physical Well Being	22.6	0.22	22.8	0.22	22.5	0.20
Functional Well Being	20.3	0.25	19.9	0.27	19.7	0.25
Ovarian Subscale	37.8	0.25	37.8	0.25	37.7	0.23
Prior to cycle 21	N=407		N=378		N=427	
TOI of FACT-O	77.6	0.73	79.1	0.71	78.6	0.66
Physical Well Being	21.7	0.26	22.3	0.25	21.9	0.23
Functional Well Being	19.4	0.28	20.1	0.28	19.6	0.25

	Arm 1		Arm 2		Arm 3	
	Mean	SE	Mean	SE	Mean	SE
Ovarian Subscale	36.7	0.30	37.1	0.30	37.2	0.28
6 months follow-up	N=362		N=347		N=375	
TOI of FACT-O	75.8	0.78	77.6	0.75	77.8	0.75
Physical Well Being	21.5	0.26	21.6	0.26	21.7	0.26
Functional Well Being	18.6	0.32	19.8	0.29	19.6	0.29
Ovarian Subscale	36.0	0.32	36.7	0.30	36.7	0.30

* The scores displayed at randomization are row scores. Note: A larger score indicates better quality of life; The scores displayed at follow-up time points are least squared means adjusted for baseline score and patient's age. QOL=Quality of life. TOI of FACT-O= Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary

Table 4

The percentage of patients reporting Abdominal Discomfort (AD) and their mean AD scores

	Regimen	No of valid assessments	Patients reporting AD (AD>0)	
			No.	% mean $\pm$ SD
Prior to Randomization	Arm 1	555	474	0.85 5.1 $\pm$ 3.4
	Arm 2	539	459	0.85 4.9 $\pm$ 3.5
	Arm3	563	470	0.83 5.2 $\pm$ 3.4
Prior to cycle 4	Arm 1	533	378	0.71 3.9 $\pm$ 2.8
	Arm 2	523	393	0.75 4.2 $\pm$ 3.1
	Arm3	527	385	0.73 4.1 $\pm$ 2.8
Prior to cycle 7	Arm 1	520	341	0.66 3.7 $\pm$ 3.1
	Arm 2	486	324	0.67 3.6 $\pm$ 2.8
	Arm3	511	321	0.63 3.7 $\pm$ 2.8
Prior to cycle 13	Arm 1	470	304	0.65 3.8 $\pm$ 3.0
	Arm 2	447	282	0.63 3.8 $\pm$ 3.1
	Arm3	463	303	0.65 3.3 $\pm$ 2.6
Prior to cycle 21	Arm 1	406	262	0.65 4.2 $\pm$ 3.3
	Arm 2	377	228	0.60 4.3 $\pm$ 3.5
	Arm3	426	279	0.65 4.1 $\pm$ 3.2
6 month follow-up	Arm 1	361	220	0.61 4.1 $\pm$ 3.1
	Arm 2	347	225	0.65 3.8 $\pm$ 2.9
	Arm3	375	232	0.62 4.3 $\pm$ 3.1