The first component of the final analysis will compare the standard arm to each of the experimental arms with respect to progression-free survival. This analysis will occur when there are at least 375 PFS events observed among those randomized to receive the standard regimen. If bevacizumab truly reduces the PFS event rate 23% then the expected number of PFS events for each of these pair-wise comparisons is 710 (335 on each experimental arm and 375 PFS events on the standard arm). The scheduling of the final analyses will coincide with the the Group's Semi-annual and Interim Meetings as previously described in the section for interim analyses.

First, the PFS event rate for each of the experimental regimens will be compared to the standard regimen, CT, with the previously described logrank test and the type I error limited to 1.35% for each test including the type I error spent for the interim analyses.

The final analysis will include an assessment of PFS in which the PFS duration will be censored at the date of the most recent radiogram for those patients who are alive and considered progression- or recurrence-free. The final analysis will also include an assessment of PFS as it is determined by the independent, blinded review (IRF), if the data are available.

The final analysis will also include exploratory analyses to assess the consistency of the treatment effect on PFS across subgroups of patients determined by presence of clinically measurable of disease (clinically measurable vs non-measurable), site of primary disease (ovarian vs extra-ovarian), stage of disease (III-optimal vs III-suboptimal vs IV), histologic cell type (papillary serous vs mucinous vs clear cell vs other cell types), Grade (1 and 2 vs 3) and age (≤ 60 vs > 60 years). The exploratory analysis also will include an estimate of the treatment hazard ratios among only those patients deemed eligible for the study.

Using logrank procedures similar to those previously described, the patients randomized to each of the bevacizumab containing treatment groups will be compared in order to assess whether the death rates are equal to the death rate of those randomized to the standard regimen.

Final analysis – (short vs prolonged treatment with bevacizumab)
In the event that both of the experimental regimens are deemed superior to the standard regimen then the two experimental regimens will be compared to each other. This analysis will be performed once there are at least 710 PFS events among those patients who were randomized to receive either CTB5 or CTB+ and survive progression-free at least 4.5 months. These treatment groups will be compared with the previously described stratified logrank test and the critical value will be set in order to limit the type I error to 0.05 including the type I error spent for interim analyses.

11.4 *Safety analyses*
The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria version 3.0 will be used to classify toxicities observed during treatment. The severity of each toxicity will be assessed according to the NCI CTCAE 3.0 grading system. Patients will be tabulated according to their maximum severity for each organ system or preferred term.

Safety endpoints will be summarized with descriptive statistics for the patients in the safety analysis dataset. The safety analysis dataset will include all patients enrolled to the study who receive any of their assigned study treatment and the patients will be grouped by their assigned treatment. Patients who do not receive any of their assigned study treatment will not be included in these analyses.

11.5 Quality of Life Analyses (08/06/07)

The principal measure used in this study to assess the quality of life (QoL) is the self-administered FACT-O TOI for ovarian cancer patients. Each patient will be asked to complete the FACT-O TOI at the following time points during their participation in the study:

11.51 Prior to cycle 1.
11.52 Prior to cycle 4 (9 weeks after starting treatment),
11.53 Prior to cycle 7 (18 weeks after staring treatment),
11.54 Prior to cycle 13 (36 weeks after starting treatment),
11.55 Prior to cycle 21 (60 weeks after starting treatment),
11.56 Six months after study treatment (84 weeks after starting treatment).
The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

Construct and content
The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QoL score. It consists of 3 subscale: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items).[93-95]

Hypotheses and analyses **(10/14/08)**
The principal QoL question is: Are the FACT-O TOI scores reported by patients at specified time points during treatment independent of the randomized treatment? This question will be broken into three separate hypotheses involving one pair of treatment groups at a time: $\mathcal{H}_{01}$: $T_{CT} = T_{CTB5}$, $\mathcal{H}_{02}$: $T_{CT} = T_{CTB+}$ and $\mathcal{H}_{03}$: $T_{CTB5} = T_{CTB+}$, where $T_{(.)}$ is a vector of mean TOI scores evaluated at specific time points for the patients treated according to the indicated treatment regimen. For the primary analysis these hypotheses will be assessed with mixed models, adjusting for pretreatment TOI score and age and patients will be included in these analyses regardless of the amount of study treatment they received. For the primary analyses patients will be categorized by their randomized treatment group rather than the treatment received. Analyses which classify patients by the actual treatment they received will be considered exploratory.

$\mathcal{H}_{01}$: $T_{CT} = T_{CTB5}$: The primary analysis comparing the self-reported TOI scores for patients receiving CT to those receiving CTB5 will focus on the scores assessed prior to cycle 4 and prior to cycle 7. These time points are considered appropriate since the immediate cumulative impact of bevacizumab treatment on TOI scores, if there is any, should be apparent by this time. Including subsequent assessments points could washout early differences between these treatment regimens, if the impact of treatment wanes after bevacizumab is stopped. It is anticipated that relatively few patients will withdraw from the study treatment prior to the 7th cycle of treatment. Since the

cumulative dose of drug in the two bevacizumab containing regimens are identical up to these points in time for the purpose of assessing this hypothesis, the mean scores for all of the patients randomized to either CTB5 or CTB+ will be combined and compared to the standard regimen (CT).

$\mathcal{H}_{02}$: $T_{CT} = T_{CTB+}$: The primary analysis comparing the self-reported TOI scores for patients receiving CT to those receiving CTB+ will focus on the scores assessed prior to cycle 13 and prior to cycle 21 (the last cycle of treatment). These time points are considered appropriate since the cumulative impact of prolonged bevacizumab treatment on TOI scores, if there is any, should be apparent by these times. This comparison will include only those patients randomized to either CT or CTB+ regardless of the amount of study treatment received.

$\mathcal{H}_{03}$: $T_{CTB5} = T_{CTB+}$: The primary analysis comparing the self-reported TOI scores for patients randomized to CTB5 to those randomized to CTB+ will focus on the scores assessed prior to cycle 13 and prior to cycle 21 (the last cycle of treatment). These time points are considered appropriate since the cumulative impact of prolonged bevacizumab treatment on TOI scores, if there is any, will be apparent by this time. This comparison will include those patients randomized to either CTB5 or CTB+ regardless of the amount of study treatment received.

Multiplicity of Outcomes
The overall type I error for these three QoL hypotheses ($\mathcal{H}_{01}$, $\mathcal{H}_{02}$, and $\mathcal{H}_{03}$) will be limited to 5% (two-tail). In order to account for multiple hypotheses, the type I error will be allocated equally to each hypothesis. Specifically, the significance level will be set to 0.0167 (0.05/3) for each treatment comparison with two-tail tests.

Missing information
Patient death, noncompliance, missed appointments, and patient illiteracy, can cause missing information. One or more of the QoL assessments may be missing for an individual on any occasion. Missing information is troublesome; particularly in studies involving repeated patient assessments. Data management procedures will be used to reduce missing data. To this end, a calendar of events which lists the dates for the required QoL assessments for each patient will be made available to the patient's health care provider as soon as the patient has been registered onto this study. Also, the clinic staff will use the GOG web-based forms tracking system to obtain reminders of the upcoming QoL assessments.

At semi-annual group meetings the data managers and nurses will be given presentations, which describe the goals of this study and stress the importance of obtaining complete assessments. A study contact person will be designated to answer questions that arise throughout the study.

Spanish and English versions of the FACT-O are available. Women who are unable to read or have difficulty reading will not be required to participate in the QoL part of this study. Also, any woman, who does not wish to participate in the QoL portion of this study, can refuse and remain eligible for the therapeutic portion of the study.

TOI Scoring

Within an individual assessment one or more items may not be answered. A subscale score will be computed as long as more than 50% of subscale items have a valid response. A subscale score S_i with N_i items will be calculated as:

$$S_i = N_i * \frac{\sum_{j=1}(\delta_{ij} * s_{ij})}{\sum_{j=1}\delta_{ij}}$$

Where δ_{ij} is equal to 1 when the jth item has a valid response, otherwise it is equal to 0 and s_{ij} is the response score of the jth item. The total FACT-O TOI score is the sum of the subscale scores.

Statistical Power Considerations
The GOG has completed a trial in which 415 patients with advanced ovarian cancer were treated with platinum and paclitaxel for 6 cycles every 21 days. These women reported their self-assessed FACT-O prior to initiating treatment, prior to the 4th cycle of treatment, following the 6th cycle of treatment and then 6 months later (GOG-172). Prior to initiating the study treatment, the mean and standard deviation of the FACT-O TOI scores were 67.2 and 15.9, respectively. The mean and standard deviation of the TOI scores prior to cycle 4, after cycle 6 and 12 months after cycle 6 were: (66.6, 15.3), (71.7, 15.6) and (82.7, 14.4), respectively. The correlation between pretreatment assessments and the assessments prior to the 4th cycles and the 6th cycle of treatment was about 0.4. The correlation between the pretreatment assessments and the assessments performed 12 months after completing treatment was 0.2.

Using these data and assuming there will be a 10% attrition of patients at each of the assessment times: prior to treatment cycle 4 and prior to cycle 7, this study is expected to have approximately 91% **(10/14/08)** power for detecting a 2.5 unit true difference in mean TOI scores between treatments when assessing $\mathcal{H}_{01}$. Similarly, assuming 20% attrition of patients prior to each treatment cycles 13 and 21, this study is expected to have approximately 90% power to detect a 3.5 **(10/14/08)** unit true difference in mean TOI scores between the treatment groups when assessing either $\mathcal{H}_{02}$ or $\mathcal{H}_{03}$. These power calculations are based on 1000 simulated trials. SAS source code for simulations is available upon request.

11.6 Genomic data analyses (08/06/07)

Overview
The overall objective of the genomic analyses is first to identify genes that are associated with longer survival and then secondly to develop a prognostic index based on the genomic data. One additional objective is to determine whether there are genomic markers that predict which patients respond favorably to bevacizumab.

In general, the primary challenges related to this objective are: a) the need to identify a relatively small number of prognostic genes from among thousands of candidate genes, b) the practicality of having a relatively small number of tissue samples relative to the number of candidate genes. In order to address these challenges this study will utilize a training dataset to develop a prognostic index and a separate and distinct validation

dataset. Also, this study will focus on the expression of a relative small number of genes (approximately 200) in which evidence from a previous study indicates that there is an association with overall survival.[96] The association between prognosis and other genes will be evaluated in a similar fashion, but these analyses will be considered part of a secondary analysis.

Training and validation sets
It is desirable to obtain tissue from all of the patients entered into the randomized portion of this trial. However, patients will not be required to submit tissue in order to participate in the randomized component of this study. In order to establish a training set this study will target a sample of sequentially enrolled eligible and evaluable patients with at least 100 deaths reported. That is, suppose 500 patients are enrolled annually onto the randomized portion of this study and 65% of these patients provide analyzable tissue for the genomic component of this study. Following a cohort of 325 patients (650*0.65) enrolled over the first year of the study for at least one additional year is expected to provide at least 100 deaths to establish the training set. The actual size of the training cohort may be adjusted depending on the proportion of patients providing analyzable tissue, but the minimum number of events will be fixed.

A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible patients with analyzable tissue and individuals will not be permitted to be members of both the training and validation cohorts.

Genomic expression: Scanning, imaging, measurement of background and spot intensities will be performed according to the Affymetrix protocol.

Preliminary analyses: Preliminary analyses will precede the primary analyses. The goal of the preliminary analyses will be to identify procedures for detecting outliers, normalizing measurements and eliminating systematic errors.[97-99]

Analysis of the training dataset: A previous study (Park, DC, unpublished manuscript) has identified approximately 200 genes in which there is some evidence of an association with overall survival in patients with high-grade, late stage ovarian cancer. The primary purpose of this analysis is to refine this set of genes and then propose a prognostic index based on the refined set of genes. Toward this end, a proportional hazards model relating expression levels of each gene to overall survival and will be fitted to the study data. In order to accommodate multiple testing with potentially correlated markers, multivariate permutation methods will be used to identify those genes that are most likely to be prognostic, while limiting the false discovery rate.[100] Specifically, each of the observed times at risk and the corresponding censoring indicator for an individual in the training set will be randomly assigned to one and only one of the expression profiles in the training set in order to define a permuted dataset. Multiple permuted datasets will be defined in a similar fashion. Then a proportional hazards model stratified on randomized treatment will be fitted to each gene using these permuted data sets. For a specified critical p-value, say ξ=0.01, the average number of false positives,ν, can be calculated from these permuted datasets. The average false discovery proportion is then ν/η_ξ where η_ξ is the number of genes with p-values less

than ξ in the original dataset. The value of ξ can be varied in order to limit the average false discovery proportion to less than a pre specified value, γ.

Conditioning the final analysis on 100 events, setting ξ=0.01 and assuming proportional hazards, this study design provides approximately a 92% chance of detecting a normally distributed marker that truly increases the failure rate 1.5 times when comparing patients whose marker values differ by one standard deviation. This design has an 85-90% chance of detecting a marker that is distributed as a gamma (shape parameter between 1 and 4 and unit variance) and truly increases the failure rate 1.4 times when comparing patients whose marker values differ by one standard deviation.

In the event that several potentially prognostic genes are identified, an unsupervised analysis like principal components analysis (PCA) (or cluster analysis) will be used to reduce the dimensionality of the gene expression data. In the case of PCA, a smaller number of variables (principal components) will be identified that captures most of the total variation in expression of the putative prognostic genes. A prediction model will then be built using these principal components and a multivariate proportional hazards model stratified by randomized treatment group.

Validation of the prognostic index: Using the coefficients from the principal components analysis and the stratified multivariate proportional hazards model developed using the training dataset, a prognostic index will be computed for each individual in the validation dataset. The independence between the prognostic index and overall survival will be assessed with a proportional hazards model fitted to the validation dataset. Ideally, the proportional hazards coefficient of the prognostic index would be 1.0. However, the degree to which this coefficient is less than 1.0 reflects the degree to which the training data was over-fitted. If the prognostic index is deemed prognostic then the relationship between the index and the time to recurrence or death can be displayed as: martingale residuals plots, Schoenfeld residual plots, ROC curves or Kaplan-Meier plots.[101]

Predictive index
A true prognostic index can be used to distinguish subgroups of patients who are likely to experience different courses in their disease. A predictive index functions similar to a prognostic index except that its function is treatment specific. For example, Her2/neu expression in breast cancers is considered a predictive marker since it predicts a favorable response to certain agents like Herceptin or tamoxifen. Biomarkers that identify biologic pathways which are necessary to respond to a particular treatment are potentially good predictive markers. The procedure for identifying predictive markers is similar to the procedure for identifying prognostics markers. However, rather than identifying markers that are associated with a particular outcome, we attempt to identify markers that are associated with the outcome only when a specific treatment is applied. In other words, in order to identify predictive genomic profiles, the procedure will focus on expression levels that significantly interact with treatment. Specifically, for each gene the proportional hazards model will include expression level, an indicator for bevacizumab and a cross product term to express an interaction between these variates. Those genes with a significant treatment interaction term are potential predictive biomarkers to be considered for defining an overall predictive index. The procedures for training, index development and validation are similar to those procedures outlined

above for prognostic factors. However, since the statistical power for detecting a predictive marker is considerable less than it is for a prognostic marker the minimum required number of events in the training and validation data will be increased.

11.7 Analyses of biomarkers for Angiogenesis

Overview of the study design

The translational research objectives of this study are to determine whether one or more biologic markers of angiogenesis are associated with either progression-free or overall survival and to develop a potentially prognostic index and possibly a predictive index.

There are several putative biomarkers for angiogenesis including: CD-31, TSP-1, CD105, vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), angiogenin, TGF-∃1, TIMP-1, TIMP-2, thrombopoietin, and VEGF-D. Some of the markers can be measured in paraffin embedded tissue, serum or both. The complete panel of angiogenic biomarkers to be included in this component of this study has not been identified yet. Some of these biomarker expression levels are assessed quantitatively while others are semi-quantitatively.

One objective of this study is to assess whether individual angiogenic biomarkers are prognostic for progression-free or overall survival. While there is no specific hypothesis proposed for this component of the study, a general design for this objective can be described. For a specific biomarker a sub sample of those patients who are enrolled, eligible and evaluable will identified. Individuals will be selected independently of their PFS or survival outcome (i.e., randomly or sequentially by date of enrollment). Generally, the size of the sub sample will be large enough to include at least 100 deaths (or PFS events) reported. However, the actual number of events may be adjusted depending on the particular hypothesis being considered or other practical considerations like laboratory costs. Assuming proportional hazards, and conditioning the analysis on 100 events provides approximately a 92% chance of detecting a normally distributed marker that truly increases the failure rate 1.4 times when comparing individuals whose marker values differ by one standard deviation and the type I error is limited to 5% for a two tail test. The hypothesis that a patient's biomarker value is independent of their overall survival (or PFS) will be assessed with a proportional hazards model. Potential confounders include: age, presence of clinically measurable of disease, site of primary disease, stage of disease, histologic cell type and grade. If a laboratory investigator proposes to evaluate 2 or 3 biomarkers simultaneously, then the design will depend on the specific study hypothesis. That is, if the biomarkers can be considered independent, then the overall type I error can be controlled for their specific study. For example, using a Bonferroni adjustment to limit the experiment-wide type I error to less than 5% for a study of 2 or 3 biomarkers (with 100 events) would reduce the statistical power for each biomarker to 86% and 78%, respectively. If the biomarkers are not considered independent, then the model and the statistical test will depend on the specific study hypothesis. When several biomarkers are studied simultaneously and there is no specific hypothesis, then a training-validation study design will be considered. This approach is described in more detail below.

A second objective of this study is to develop a prognostic index utilizing several biomarker measurements from samples collected prior to study treatment. An additional objective is to develop a predictive index. It is hoped that the predictive

index will identify those patients most likely to benefit from the addition of bevacizumab therapy.

The overall approach for this study is to develop a prognostic (and predictive) index by modeling the data from a training data set and then validate the index in an independent data set. The modeling procedures for developing a prognostic index are described in the following paragraphs. The procedures for developing a predictive index are similar.

Description of the training and validation data sets
The patients registered to this study will be allocated to either a training data set or a validation data set. The training and validation datasets will consist of cohorts of sequentially enrolled eligible and evaluable patients. For practical reasons individuals entering the study early will be assigned to the training data set, while those entering the study later will be allocated to the validation data set.

The training data set will be considered sufficiently mature to permit developing a prognostic index from the proposed list of markers when there are at least 100 deaths among the first cohort of sequentially enrolled eligible and evaluable patients.

Screening markers of angiogenesis
The first step toward evaluating these biomarkers is to assess the distribution of each biomarker and the correlation between pairs of biomarkers. Biomarker values that appear to be extreme outliners will be investigated to determine whether there were any anomalies in the handling or processing of the specimen, which may explain the extreme values. Also, highly correlated biomarkers will be noted since these can introduce anomalies into the modeling procedures.

In order to visually assess the univariate relationship between each biomarker value and relative death rates, the marker values will be plotted against martingale residuals from a proportional hazards model that does not include the biomarker as a covariate. The martingale residuals may be smoothed over biomarker values with either piece-wise cubic polynomials, penalized curve fitting or kernel smoothers. These plots will be used to detect departures from linearity and to assess when a more complex model may be necessary to describe the relationship between biomarker values and log hazard ratio. Cross-validation, bootstrapping or a penalized likelihood function will be used to judge the maximum degree of complexity to be considered. If restricted cubic regression splines are used, then functions with not more than four degrees of freedom should be sufficiently flexible to model most relationships. For those pairs of covariates that are highly correlated, consideration will be given to using functional transformations of these markers. For example, a simple approach would use the sum and the difference highly correlated biomarkers for each individual in a proportional hazards model, since these correspond to the first and second principle components for the pair of biomarkers.

A plot of beta residuals can be used to assess the influence of each individual on the estimated log hazard ratio. These plots can be used to identify individuals with an unusually large influence. These individuals will be investigated to determine whether there were any anomalies in the handling or processing of the specimen that may explain the unusual values.

Multivariate model
Using the functional relationships between the biomarker values and the log relative hazards developed during the biomarker screening step, a multivariate model will be constructed. Biomarkers will be eliminated from the model in order to identify a parsimonious model that appears to have some predicative value but is not overly complex. Cross-validation, bootstrapping or a penalized likelihood function will be used to judge parsimony.

Covariate Interactions
For the purposes of building a prognostic index, only first-order covariate interactions that have a biologic rationale will be considered. That is, if a particular laboratory assay measures a receptor then modeling interactions with potential ligands will be considered. In this case, it is reasonable to expect that the prognostic value of a ligand may depend on the presence of receptors in the tumor. The evaluation of second-order or higher interactions will not be evaluated at this point but considered in exploratory analyses (see below). Biologically, a second-order interaction could exist when two different ligands compete for the same receptor and one switches on and the other switches off cell growth.

A covariate may also interact with time. That is, the effect size may depend on the follow-up time. Schoenfeld residual plots vs time are useful for identifying these types of interactions. Fitting the Schoenfeld residuals over time with either piece-wise cubic polynomials, penalized likelihood regression or kernel smoothers may be used to visualize departures from proportional hazards.

Missing values
It is anticipated that there will not be a significant number of missing biomarker values. Nevertheless, eliminating individuals due to partially missing biomarker values is not desirable, since this may introduce bias or artificially reduce the variance of the biomarker. Therefore, procedures for handling missing values may be necessary. Provided no more than 10% of the values for a particular biomarker are missing, values imputed from the available values can be used. If missing values account for more than 10%, but not more than 20% of the measures for a particular biomarker, then conditional imputation, which considers the correlation with other biomarkers, will be considered. Finally, if 20% or more of the values for a particular biomarker are missing, multiple imputations can be used to characterize the additional uncertainty in the parameter estimates due to incorporating imputed values in place of unknown values.

External validation
A prognostic score for each individual in the validation dataset will be computed using the parameter estimates obtained from modeling of the training data set. This score will be modeled with a proportional hazards model in the validation data set. The coefficient estimated from this later model provides an unbiased measure of the value of the prognostic score. If the validation data set includes 100 deaths (or PFS events), then this sample size provides a 92% chance of correctly classifying an index as predictive if those individuals whose index values are separated by one standard deviation have an associated 1.4-fold increase in their death rate.

Exploratory analyses

While the procedure for building a prognostic score outlined above has flexibility, it is somewhat constrained in order to avoid over-fitting the data in the training set. Over-fitting leads to poor prediction and reduces the external validity of the prognostic score. It is not possible, however, to devise a modeling strategy that consistently produces the 'best' prognostic score. Therefore, exploratory analyses will be performed using alternative model building strategies to identify better prognostic scores. One alternative modeling approach is to first reduce the dimensionality of the data with cluster analyses or principal component analysis. In order to avoid bias, it is important that subsequent data modeling procedures do not incorporate any information from the validation dataset. The prognostic score from subsequent models will be assessed relative to the prognostic score developed from the proposed strategy. The c-index computed in the validation data set will be used to compare alternative prognostic scoring procedures. The c-index is the probability that the survival times from two individuals randomly selected from the validation data set can be correctly ranked based on their prognostic scores. A c-index value of 0.5 indicates that the prognostic index is useless, while a value equal to 1.0 indicates a perfect prognostic index. Occasionally, the c-index is transformed so that $D_{xy} = 2*(\text{c-index} - 0.5)$. This index ranges from 0 to 1 and it is analogous to the Somers rank correlation index for censored data.

Predictive index

A prognostic index is used to identify those patients who at greater (or lesser) risk of experiencing a specific clinical event. A predictive index is similar to a prognostic index, but depends it also depends on the prescribed treatment. For example, stage is a prognostic factor for patients with breast caner, and estrogen receptor status is a predictive factor since it identifies those patients who are more or less likely to respond to hormonal treatments. One additional goal for this study is to develop a predictive index from the markers of angiogenesis. That is, the focus of the analysis is to determine those markers that are associated with prognosis provided that the patient received bevacizumab. Therefore, rather than assess the main association between a biomarker and log relative hazard described previously, the proportional hazards model will assess the interaction between biomarker and bevacizumab treatment when a predictive index is being developed.

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