Supplementary Figure Legends

Supplementary Figure 1: Differences in AGP, mesothelin and FLT4 concentrations between responders and non responders in the discovery sample set (n=10). Mass spectrometry label-free quantitation of AGP, mesothelin and FLT4 levels in responders (R) and non responders (NR) from the experimental arm of the trial at time points 1 (baseline) (T1) and 4 (pre-cycle 2) (T4) together with corresponding data as measured using immunoassays. Graphs show mean +/- SEM. For AGP the immunoassay measured both AGP1 and 2.

Supplementary Figure 2: Progression-free survival in validation cohort I. (a) Kaplan-Meier (KM) estimates of the survival functions in the standard arm and experimental arm of the trial in validation cohort I and (b) plot of differences in the KM survival function reveals the existence of non-proportional hazards over time in validation cohort I, similar to that seen in the overall trial population.

Supplementary Figure 3: Baseline concentrations of mesothelin, FLT4, AGP and CA125 in: a). validation cohort I, b). validation cohort II, and c). both validation cohorts combined. Values are shown for patients in each arm of the trial (CP or CP plus bevacizumab) and subdivided into whether low or high risk. The solid red lines show the median values for each and the dashed red lines show the upper limit of the normal range, as described in the Methods section, for each analyte. In the case of AGP the upper limit of normal for both females>50 years of age (upper line) and <50 years are shown (lower line).

Supplementary Figure 4: Correlation between biomarkers investigated in validation cohort I. Correlogram demonstrating correlation between potential biomarkers using all available samples from validation cohort I.

Supplementary Figure 5: Longitudinal patterns in AGP concentration in validation cohort I. (a) Longitudinal box plots* showing changes in AGP median concentration over time points in TRICON7 sampling scheme. Panels show progressors and non-progressors in terms of PFS in standard and experimental arms of trial and (b) longitudinal patterns in AGP by risk of progression status (as above but split by risk of progression, defined as patients with FIGO stage IV disease OR FIGO stage III disease AND >1.0 cm residual disease after debulking surgery).

*Box plots show median, interquartile range (IQR) and 1.5×IQR. Dots represent outliers (defined as greater/less than 1.5×IQR).
Supplementary Figure 6. Prognostic and predictive potential of candidate biomarkers in validation cohort I. Kaplan-Meier estimates of survival functions for biomarkers at baseline (time point 1) dichotomized at optimum cut-points (derived by maximising Harrell’s C-index) in all patients (column a), standard arm (column b), experimental arm (column c) and for all patients with interaction for treatment group included in the model (column d). Chi-squared results and associated p-values from log-rank tests to compare survival curves shown on all plots. Hazard ratios for interaction term for predictive ability and associated p-value is also displayed in column d.

Supplementary Figure 7. Kaplan Meier estimates of the survival function showing prognostic and predictive ability of the biomarker index in validation cohort I. (a) Kaplan Meier estimates of the survival function for the biomarker index showing weak evidence of association with prognosis, i.e. the prognosis is worse for patients as the biomarker index increases and (b) Kaplan Meier estimates of the survival function for the biomarker index with index scores separated by treatment received, the log rank test shows strong evidence that the survival curves are not identical (p=0.018) and the predictive potential of the index (and hence the departure from additivity in effect) is demonstrated through the change in order of the solid and dashed curves in the plot from the top of the plot to the bottom, e.g. the red curves are largely overlapping; the green curves show dashed line above solid line whereas the blue and yellow curves show solid lines above dashed lines.

Supplementary Figure 8. Prognostic and predictive potential of individual elements of biomarker index in the combined validation cohort. Kaplan-Meier estimates of survival functions for individual elements of the biomarker index dichotomized at optimum index cut-point in all patients (column a), standard arm (column b), experimental arm (column c) and for all patients with interaction for treatment group included in the model (column d). Chi-squared results and associated p-values from log-rank tests to compare survival curves shown on all plots. Hazard ratios for interaction term for predictive ability and associated p-value is also displayed in column d.