Aim: Bevacizumab improves progression-free survival in advanced stage ovarian cancer patients treated with carboplatin and paclitaxel. We evaluated the role of genetic variants in modifying the benefit of bevacizumab in ICON7, one of the key clinical trials to describe this benefit in ovarian cancer. Using a hypothesis-agnostic genome-wide association study (GWAS) approach, we evaluated association of genetic markers with survival.

Methods: Germline DNA from 437 patients were genotyped using an Illumina Omni-Platform. In an interaction analysis, Cox proportional hazard models of overall survival generated P-values for bevacizumab-polymorphism interaction terms. We further described the interactions by assessing treatment arm-specific hazard ratios and 95% confidence intervals adjusted for clinical prognostic factors. Likelihood ratio tests were performed comparing models with and without the interaction term; an additive genetic inheritance model was assumed.

Results: After quality control steps, 400 patient samples and 727,683 markers were evaluable. Median follow-up was 2.1 years, with 22% deaths. After adjusting for treatment arm, country, FIGO stage, and treatment initiation time relative to diagnosis, no single marker reached global GWAS significance. The top markers associated with overall survival were in the CD26 gene family, with the top genetic variants had an interaction P value of 2.3x10^{-6}. For an increase in each minor allele, there was an increase in risk of death in patients treated with the standard chemotherapy arm (adjusted aHR, 2.55 (95% CI: 1.7-3.9). In contrast, in the bevacizumab-treatment arm, the corresponding aHR was 0.64 (95%CI:0.4-1.0). This family of molecules has been associated with angiogenesis and epithelial ovarian cancer through its link with CXC chemokine activity.

Conclusions: Novel genetic markers in the CD26 family were associated with bevacizumab-related survival in the ICON7 trial. Validation in other bevacizumab treatment trials is warranted.

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