Genome-wide association studies of survival in 1,520 cancer patients treated with bevacizumab-containing regimens

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Supplementary Table and Figures

Table S1. Results of the association between SNPs and OS as a prognostic effect and as a predictive effect for each study. Rows in bold are those with p-value<0.05 in at least three out of four trials. *NA* SNP not present in the genotyping platform of the trial.

	CALGB 80303			CALGB 40503			CALGB 80405			ICON7		
Prognostic effect												
SNP	**p-value**	**Effect size (β)**	**HR (95% CI)**	**p-value**	**Effect size (β)**	**HR (95% CI)**	**p-value**	**Effect size (β)**	**HR (95% CI)**	**p-value**	**Effect size (β)**	**HR (95% CI)**
rs680949	**0.0340**	**0.34**	**1.40 (1.03-1.92)**	**0.0357**	**0.59**	**1.80 (1.04-3.12)**	**0.0004**	**0.44**	**1.55 (1.21-1.97)**	**0.0035**	**0.65**	**1.92 (1.24-2.99)**
rs218527	**0.0039**	**0.44**	**1.56 (1.15-2.10)**	**0.0281**	**0.43**	**1.53 (1.05-2.25)**	**$4.8x10^{-5}$**	**0.44**	**1.55 (1.26-1.92)**	**0.6642**	**0.09**	**1.09 (0.74-1.62)**
rs2795492	0.0466	-0.17	0.84 (0.71-1.00)	0.2723	-0.16	0.85 (0.64-1.14)	$1.6x10^{-5}$	-0.30	0.74 (0.65-0.85)	0.7248	-0.05	0.95 (0.72-1.25)
rs476612	**NA**	**NA**	**NA**	**0.0357**	**0.59**	**1.80 (1.04-3.12)**	**0.0060**	**0.44**	**1.55 (1.13-2.11)**	**0.0035**	**0.65**	**1.91 (1.24-2.94)**
rs7615734	0.0015	0.37	1.45 (1.15-1.83)	0.0816	0.31	1.36 (0.96-1.93)	0.0024	0.24	1.28 (1.09-1.50)	0.8265	0.04	1.04 (0.75-1.44)
rs6712389	NA	NA	NA	0.1487	-0.23	0.80 (0.58-1.09)	0.0001	-0.29	0.75 (0.65-0.87)	0.0963	-0.28	0.76 (0.54-1.05)
rs16852804	0.0018	0.52	1.68 (1.21-2.34)	0.0667	0.40	1.50 (0.97-2.30)	0.0751	0.29	1.33 (0.97-1.82)	0.0536	0.48	1.61 (0.99-2.62)
rs10950639	NA	NA	NA	0.0788	0.32	1.37 (0.96-1.95)	0.0004	0.28	1.32 (1.13-1.55)	0.0722	0.29	1.34 (0.97-1.85)
rs4807493	0.0009	-0.33	0.72 (0.59-0.87)	0.8503	0.03	1.03 (0.74-1.43)	0.0029	-0.26	0.77 (0.65-0.92)	0.2037	-0.24	0.79 (0.54-1.14)
rs2103445	NA	NA	NA	0.0176	0.35	1.42 (1.06-1.89)	0.0004	0.26	1.29 (1.12-1.49)	0.4325	0.13	1.13 (0.83-1.55)
Predictive effect												
SNP	**p-value**	**Effect size (β)**		**p-value**	**Effect size (β)**		**p-value**	**Effect size (β)**		**p-value**	**Effect size (β)**	
rs4969481	0.0093	-0.66		0.1896	-0.45		$2.4x10^{-5}$	-0.80		0.1114	-0.71	
rs11895736	0.1429	-0.38		0.1474	-0.61		$1.6x10^{-5}$	-0.83		0.0497	-0.81	
rs448960	NA	NA		0.1462	-0.41		0.0004	-0.60		0.0161	-0.70	
rs10763269	0.0001	0.80		0.1134	0.52		0.0730	0.28		0.1595	0.49	
rs13392750	NA	NA		0.0183	0.68		0.0003	0.63		0.2677	-0.32	
rs3795897	**0.0101**	**0.64**		**0.2479**	**0.47**		**0.0333**	**0.59**		**0.0037**	**1.22**	
rs1150743	0.0027	0.83		0.0938	0.85		0.0148	0.52		0.2130	0.64	
rs10915428	0.2065	-0.22		0.3642	-0.27		0.0000	0.52		0.2259	-0.34	
rs11860804	NA	NA		0.7598	-0.10		0.0001	-0.53		0.0214	-0.64	
rs6453031	NA	NA		0.3486	-0.34		0.0002	-0.65		0.0304	-0.88	

Table S2. Results of the association between prognostic SNPs and OS in TCGA patients. SNPs in bold are those tested for association. P-values in bold are for SNPs that replicated in TCGA. *TCGA* The Cancer Genome Atlas, *COAD* colon adenocarcinoma, *READ* rectum adenocarcinoma, *OV* ovarian serous cystadenocarcinoma, *LD* linkage disequilibrium, *MAF* minor allele frequency, *NA* Intergenic SNP, *HR* hazard ratio, *CI* confidence interval.

SNP	Gene	Genotyped in TCGA	SNP in LD (proxy)	MAF (COAD+READ / OV)	p-value (COAD+READ / OV)	HR (95% CI) (COAD+READ / OV)	p-value (meta-analysis)	HR (95% CI) (meta-analysis)
rs680949	***PRUNE2***	Yes	-	0.11 / 0.12	0.0529 / 0.1860	1.76 (0.99-3.11) / 1.44 (0.84-2.48)	**0.0219**	**1.58 (1.07-2.35)**
rs218527	NA	No	**rs218529** (R^2=1.0)	0.11 /0.10	0.0687 / 0.0493	0.37 (0.13-1.08) / 1.84 (1.00-3.36)	0.4990	1.16 (0.75-1.79)
rs2795492	*CORO2A*	No	rs2250494 (R^2=0.57)	-	-	-	-	-
rs476612	*LOC100129762*	No	rs680949 (R^2=1.0)	-	-	-	-	-
rs7615734	NA	Yes	-	0.17 / 0.25	0.2984 / 0.4110	0.72 (0.39-1.34) / 1.19 (0.82-1.41)	0.2446	1.22 (0.87-1.72)
rs6712389	NA	No	**rs10490715** (R^2=1.0)	0.22 / 0.35	0.4197 / 0.3200	1.29 (0.69-2.41) / 1.20 (0.84-1.72)	0.2062	1.22 (0.90-1.67)
rs16852804	*BARD1*	No	**rs16852802** (R^2=1.0)	0.02 / 0.08	0.0127 / 0.0026	5.09 (1.41-18.33) / 2.71 (1.42-5.20)	**$1.39x10^{-4}$**	**3.09 (1.73-5.51)**
rs10950639	NA	Yes	-	0.27 / 0.24	0.9284 / 0.4810	1.03 (0.57-1.83) / 1.16 (0.76-1.78)	0.5347	1.11 (0.79-1.57)
rs4807493	*PIP5K1C*	No	rs7253265 (R^2=0.42)	-	-	-	-	-
rs2103445	NA	Yes	-	0.28 / 0.31	0.3320 / 0.8400	0.75 (0.42-1.34) / 0.96 (0.67-1.39)	0.4888	0.90 (0.66-1.22)

Fig. S1 CONSORT and quality control flowchart for CALGB 80303, 40503, 80405, and ICON7. *MAF* minor allele frequency; *HWE* Hardy-Weinberg Equilibrium.

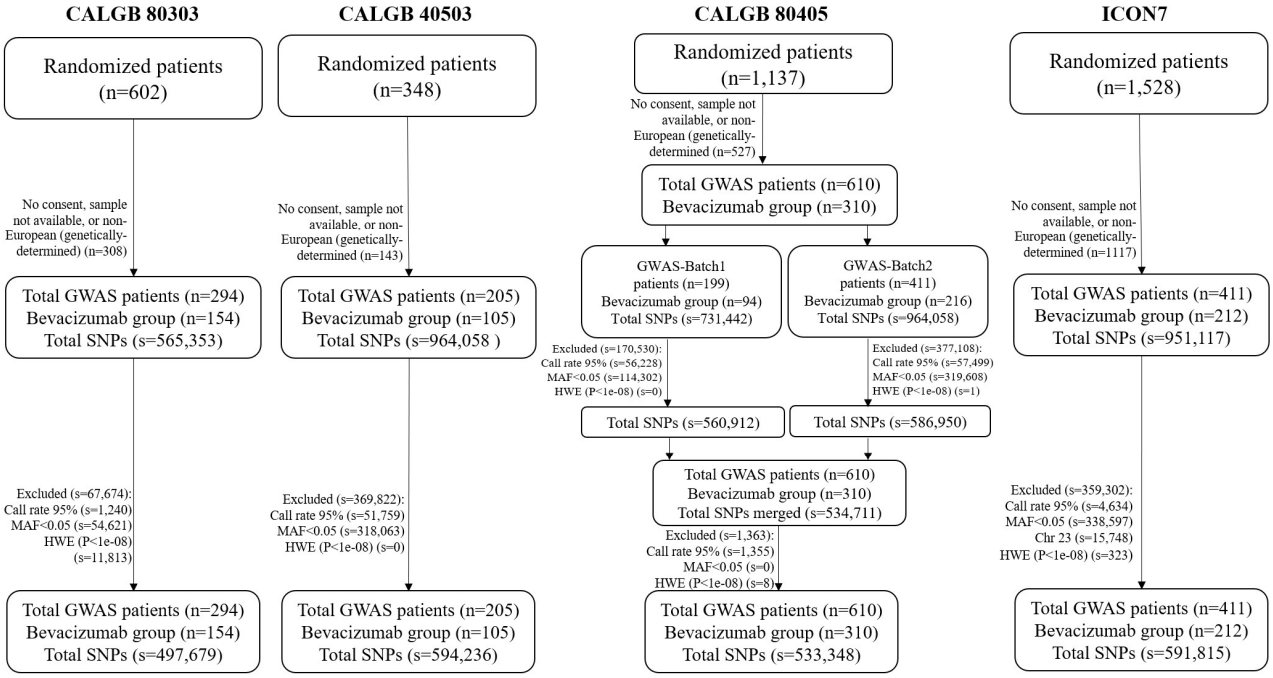
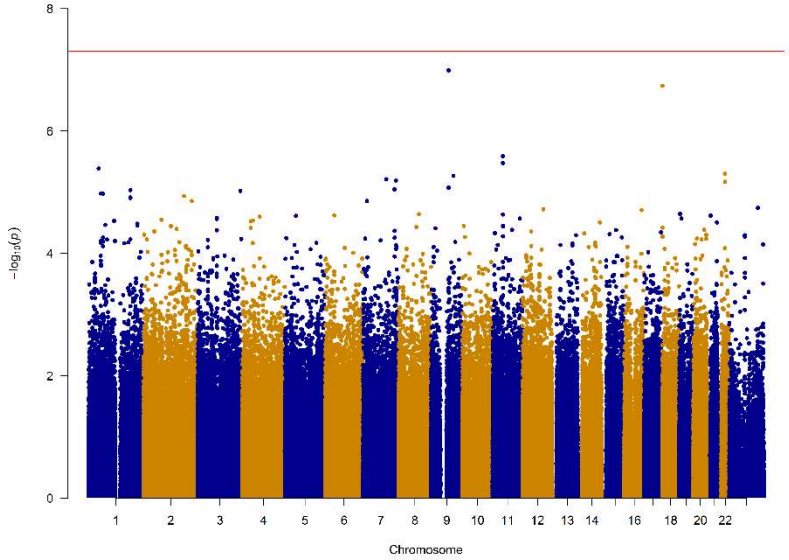
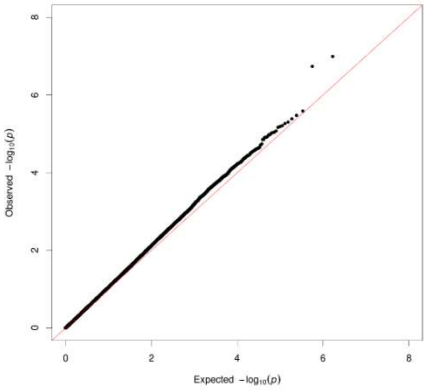


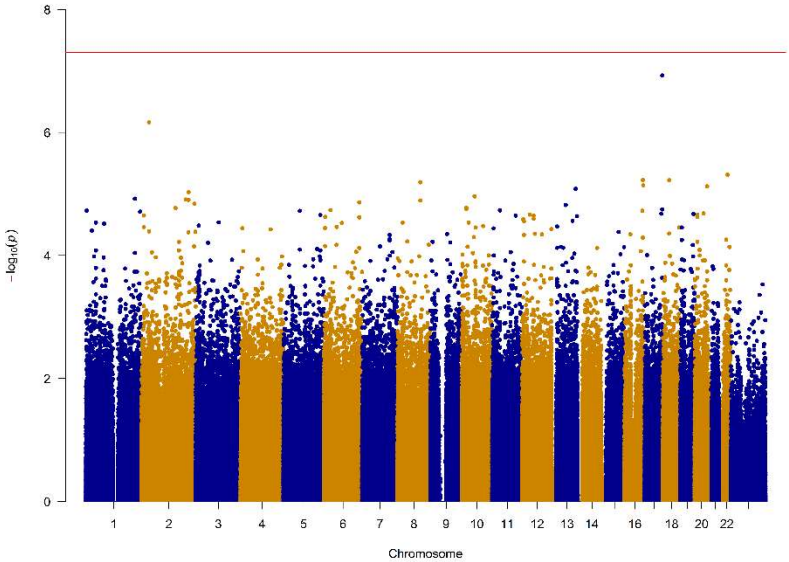
Fig. S2 Manhattan plot (left) and quantile-quantile (Q-Q) plot (right) from SNP-based association results.

Prognostic effect





Predictive effect



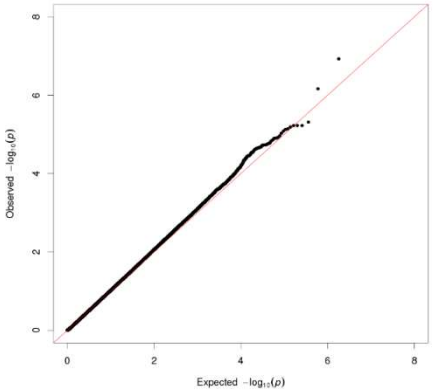
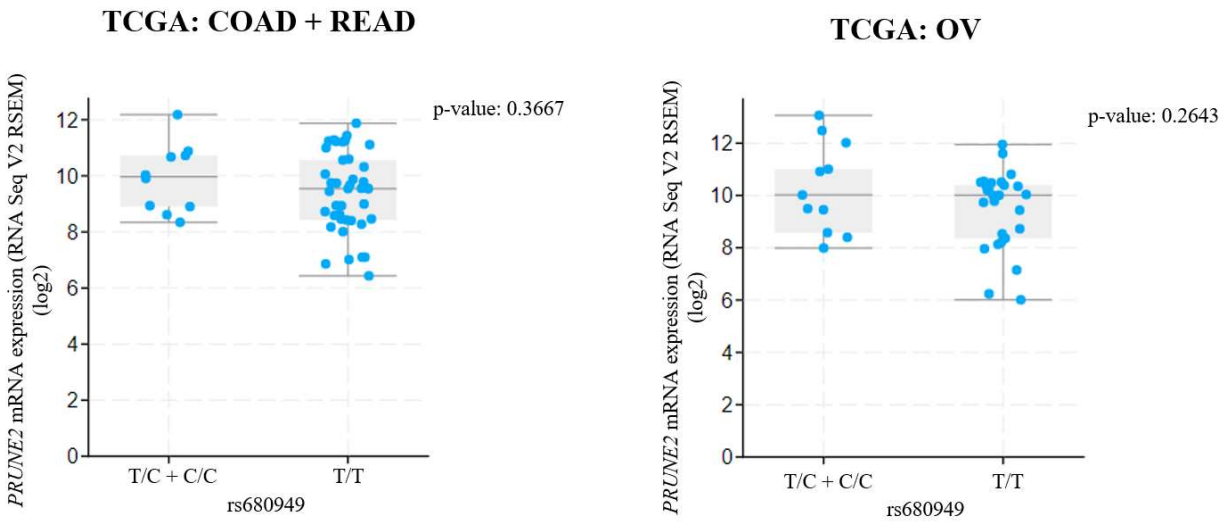


Fig. S3 Association between (A) *PRUNE2* and (B) *BARD1* mRNA expression and SNPs in COAD+READ and OV patients from TCGA.

(A) *PRUNE2*



(B) *BARD1*

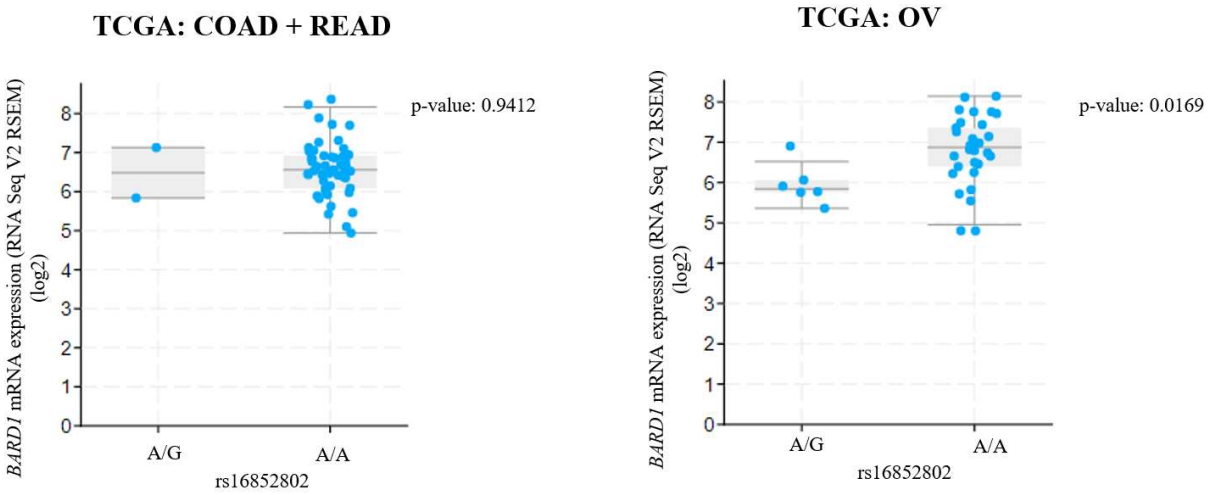


Fig. S4 Position of rs680949 (T>C/A>G) in *PRUNE2* relative to the Myc transcription factor binding motif and effect of the allele change (T versus C). Sequence logo from atSNP representing the JASPAR positional weight matrix of the Myc binding motif. The sequence of the putative regulatory region surrounding rs680949 (highlighted in gray), with the minor allele (C, top) or reference allele (T, bottom), is shown overlapping the JASPAR Myc binding motif. The height of the bases indicates the level of conservation across species, suggesting a regulatory role. rs680949 results in a nucleotide change from T to C in a conserved region of the Myc binding motif.

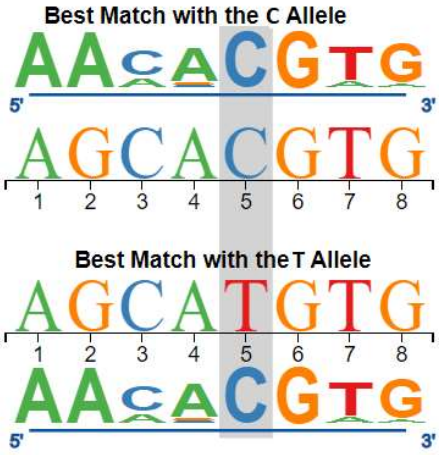


Fig. S5 Association of rs368962482 (G>A, complete LD, R^2=1.0, with rs16852804) with *BARD1* mRNA expression in monocytes. Median, 25th and 75th percentiles, minimum and maximum values of *BARD1* transcripts per million (TPM). Data from the Database of Immune Cell eQTLs (DICE).

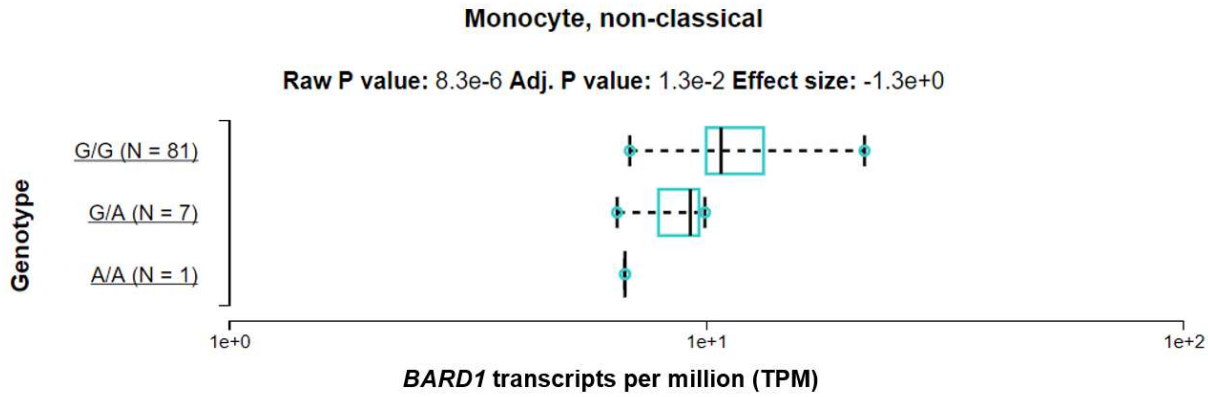


Fig. S6 Kaplan-Meier estimates of OS for rs3795897 in *AGAP1* (G>A, MAF 0.11-0.17), predictive effect. *genotyped only in patients from the GWAS-Batch 1 (n=199, **Fig. S1**). *CALGB* Cancer and Leukemia Group B, *ICON7* International Collaboration on Ovarian Neoplasms; *OS* overall survival; *CI* confidence interval; *NR* not reached.