

Supplementary figures

Figure S1. Comparison of HER2 and CDH1 mRNA expression levels with HER2-positivity (A) and E-CAD immunohistochemical evaluation (B) in the same tumor cases. The median *HER2* mRNA expression level was strongly increased in the HER-POS group, Kruskal-Wallis, $P < 0.001$. The median *CDH1* mRNA expression level increased in patients with E-cadherin score 2 compared with those having a reduced E-cadherin expression (score 1) and much more with those having a low E-cadherin expression (score 0) at immunohistochemical staining. Kruskal-Wallis, $P = 0.039$, Jonckheere trend test, $P = 0.035$.

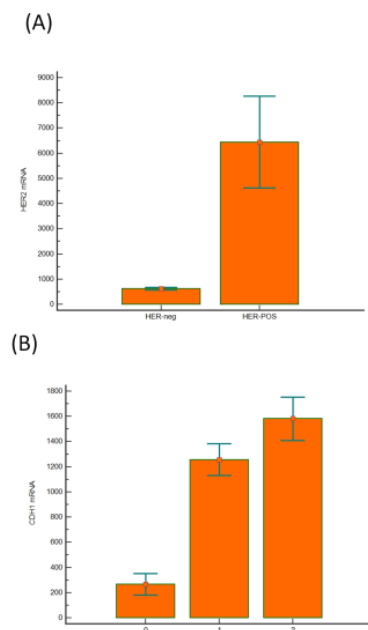
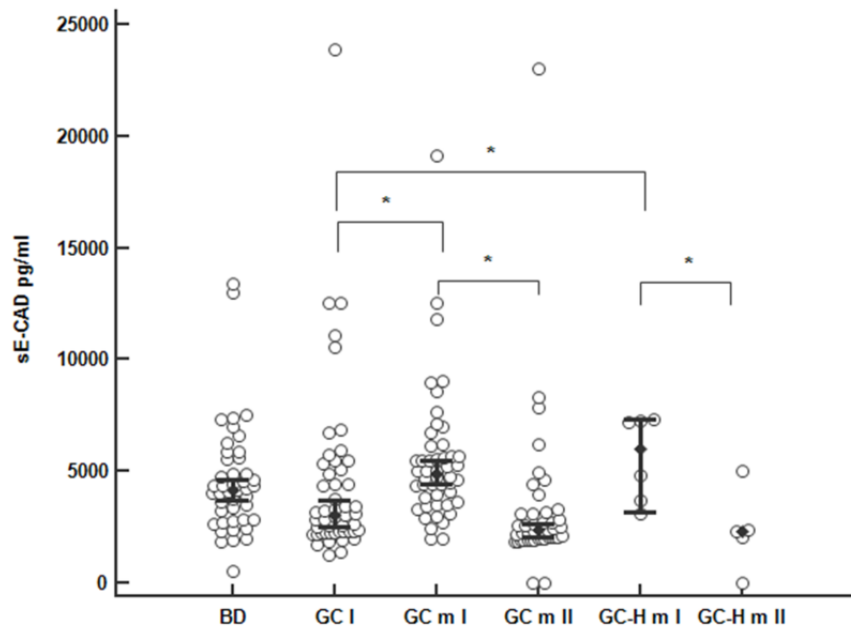


Figure S2. a) Distribution of serum sE-CAD in blood donors (BD, $n = 44$) and in patients with GC ($n = 94$). The median serum levels of sE-CAD were elevated in both HER2-neg mGC (4885 pg/ml) and HER2-Pos mGC (6001 pg/ml), and they were similar between BD (4187 pg/ml) and GC without metastasis (3033 pg/ml). After treatment, the concentration of sE-CAD decreased in both the mGC groups [Difference prior and after treatment: HER2-negative: GC m I vs GC m II: -2541, (95%CI -3567 to -1100); HER2-positive: GC-H m I vs GC-H m II: -3667 (95%CI -5791 to -639)].

sCDH1, soluble E-cadherin form; GC I, GC without metastasis ($n = 49$), GC m I, HER2-negative metastatic GC before treatment ($n = 49$), GC-H m I HER2-positive metastatic GC before treatment ($n = 6$), GC-H m II, HER2-negative metastatic GC after 3 weeks of the initial treatment ($n = 42$); GC-H m II, HER2-positive metastatic GC after 3 weeks of the initial treatment ($n = 5$). *, $p < 0.05$.

b) Distribution of serum sE-CAD in the same groups of patients according to the rs16260 variants.

a)



b)

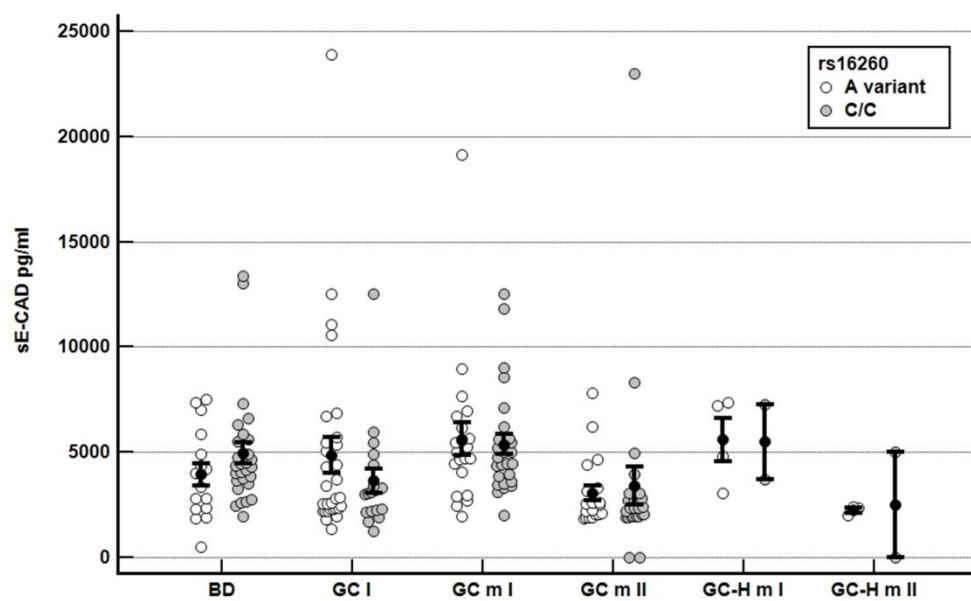
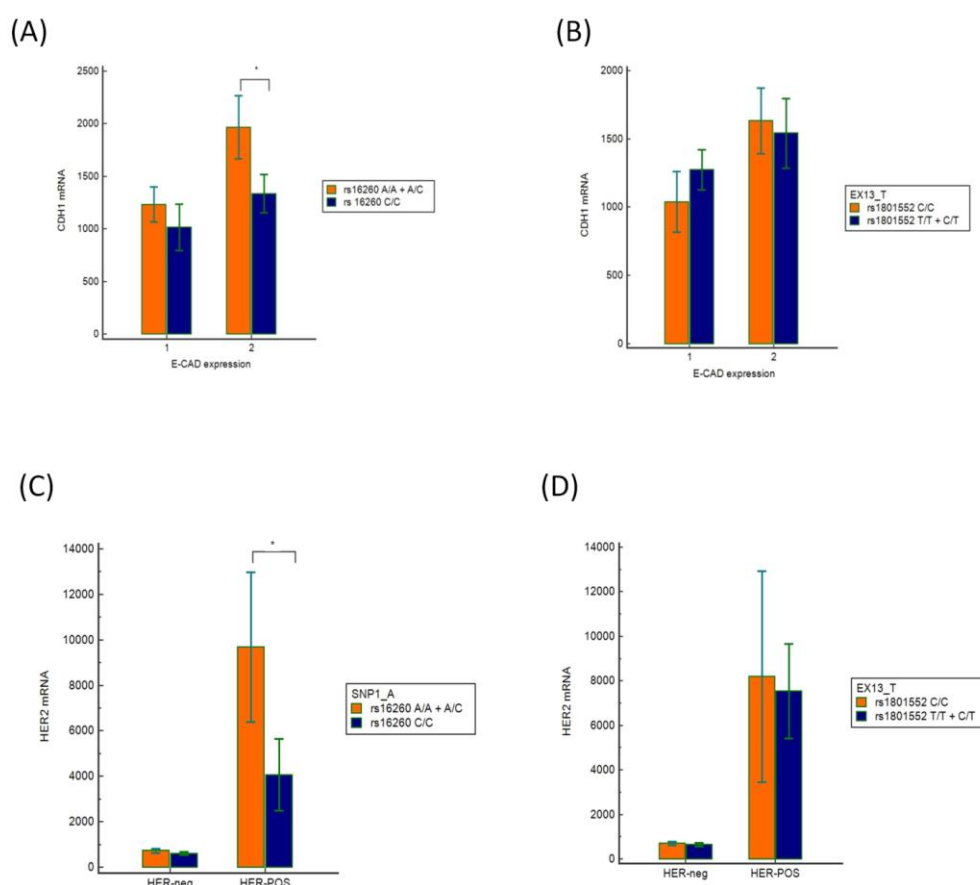


Figure S3. The Median expression of *CDH1* mRNA level increased in patients having simultaneously the rs16260-A variant (A/A + A/C genotype) and high E-CAD expression (IHC staining score 2) (**A**, $P < 0.05$). In the same way, the median expression of HER2 mRNA level increased in patients having simultaneously the rs16260-A variant (A/A + A/C genotype) and high HER2 expression (HER2-POS) (**C**, $P < 0.05$). Neither the *CDH1* mRNA expression levels nor the HER2 mRNA reached any statistical difference in change concerning *CDH1* rs1801552 genotypes (**B**, **D**) (Two way Anova tests). the number of patients with rs16260 A variant was higher in the HER2-positive than in HER2-negative mGC patients (11 of 24, 45.8% and 7 of 24, 29.1%, respectively). The number of patients with rs16260 A variant was higher in the HER2-positive than in HER2-negative mGC patients (11 of 24, 45.8% and 7 of 24, 29.1%, respectively) (**E**). HER2-negative mGC, patients having the wild type *CDH1* (rs16260 C/C) showed a reduced survival compared to patients with HER2-positive (**F**).



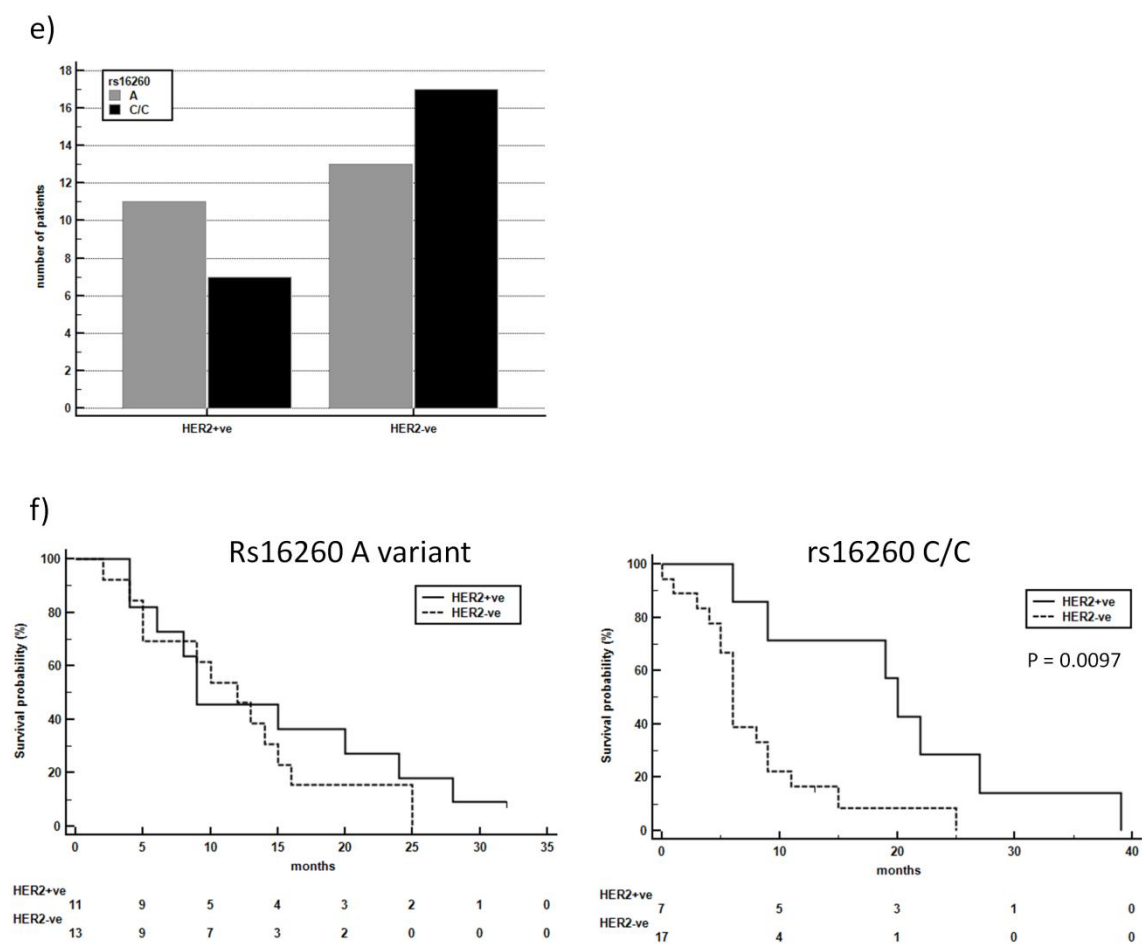


Figure S4. String protein-protein interaction network covering genes we found specifically associated with mRNA HER2-overexpressed GC (i.e. *RPL19*, *KLRG1*, *RARA*, *ZEB1*, *SNAI2*, *CDH1*, and *EGF*)

