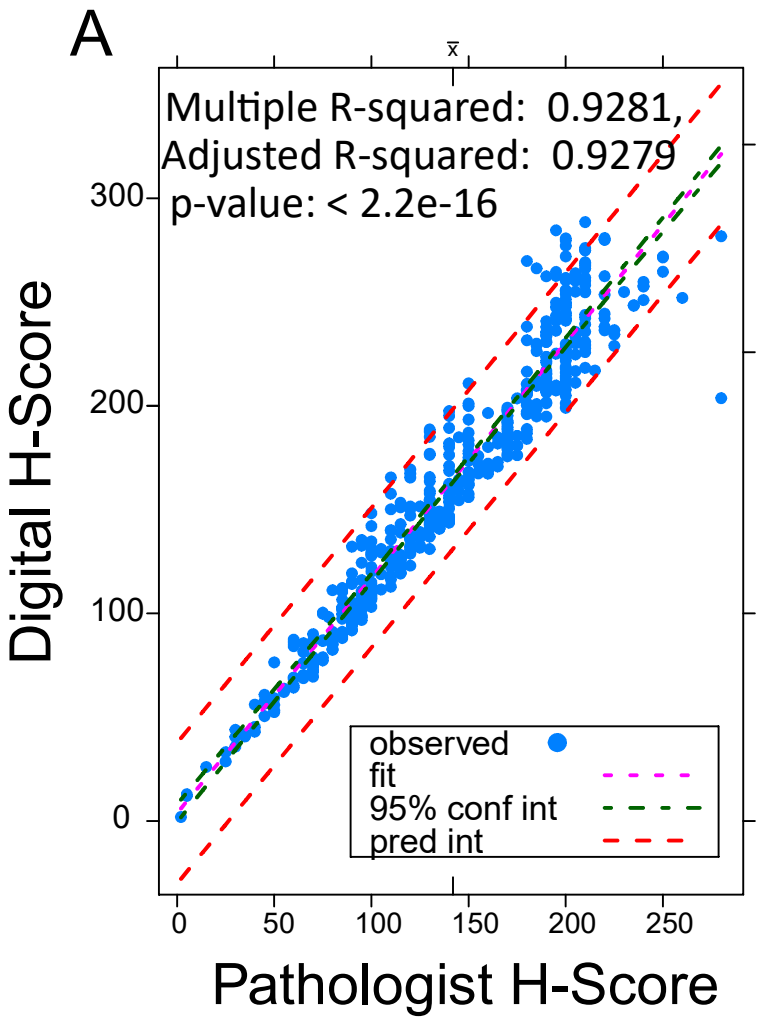
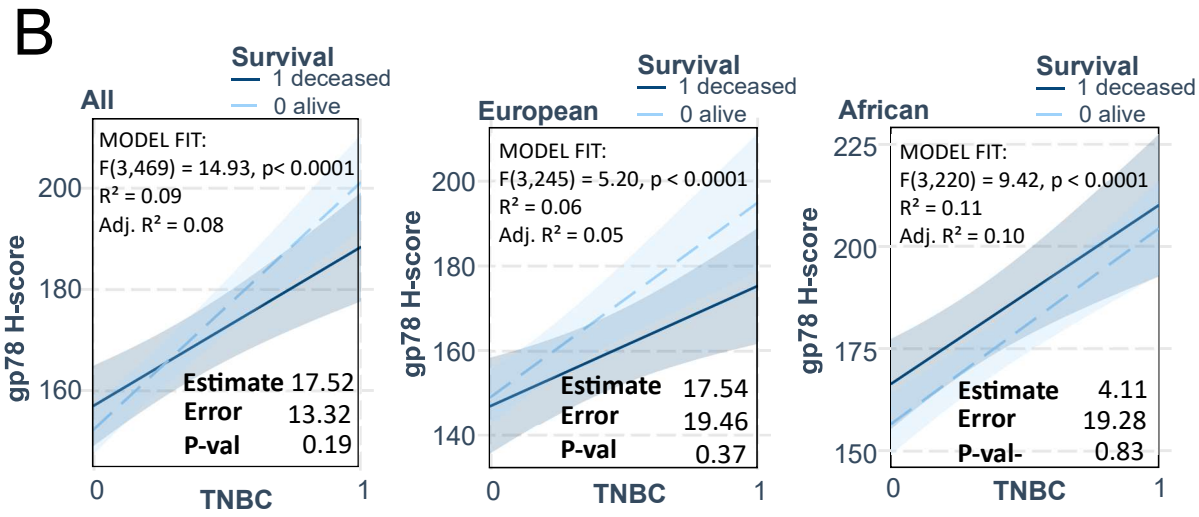



C

**ALL**

| Interaction | Estimate | Std. Error | t-value | Pr(>\|t\|) |
|---|---|---|---|---|
| TNBC | 48.97 | 8.29 | 5.91 | <0.0001 |
| Survival | 4.73 | 7.29 | 0.65 | 0.52 |
| TNBC: Survival | -17.52 | 13.32 | -1.31 | 0.19 |

**European**

| Interaction | Estimate | Std. Error | t-value | Pr(>\|t\|) |
|---|---|---|---|---|
| TNBC | 45.87 | 13.67 | 3.35 | <0.0001 |
| Survival | -2.04 | 10.22 | -0.2 | 0.84 |
| TNBC: Survival | -17.54 | 19.46 | -0.9 | 0.37 |

**African**

| Interaction | Estimate | Std. Error | t-value | Pr(>\|t\|) |
|---|---|---|---|---|
| TNBC | 48.97 | 8.29 | 5.91 | <0.0001 |
| Survival | 9.78 | 10.38 | 0.94 | 0.35 |
| TNBC:Survival | -4.11 | 19.28 | -0.21 | 0.83 |

**Supplementary Figure 1:** Correlation between gp78 digital score and pathologists score and interaction between gp78 digital score and TNBC subtype. (**A**) Correlation is shown between digital and pathologists scores using both multiple and adjusted correlations with p-value and 95% confidence interval provided. (**B**) ( right) Interaction curves showing that the relationship between gp78, TNBC, and survival in the total cohort (ALL) compared to women of European versus African ancestry demonstrating a greater interaction between TNBC and survival in European patients compared to patients of African ancestry. (**C**) Table showing that TNBC subtype is influenced by survival in the total cohort and women of European descent, but much less so in women of African ancestry.

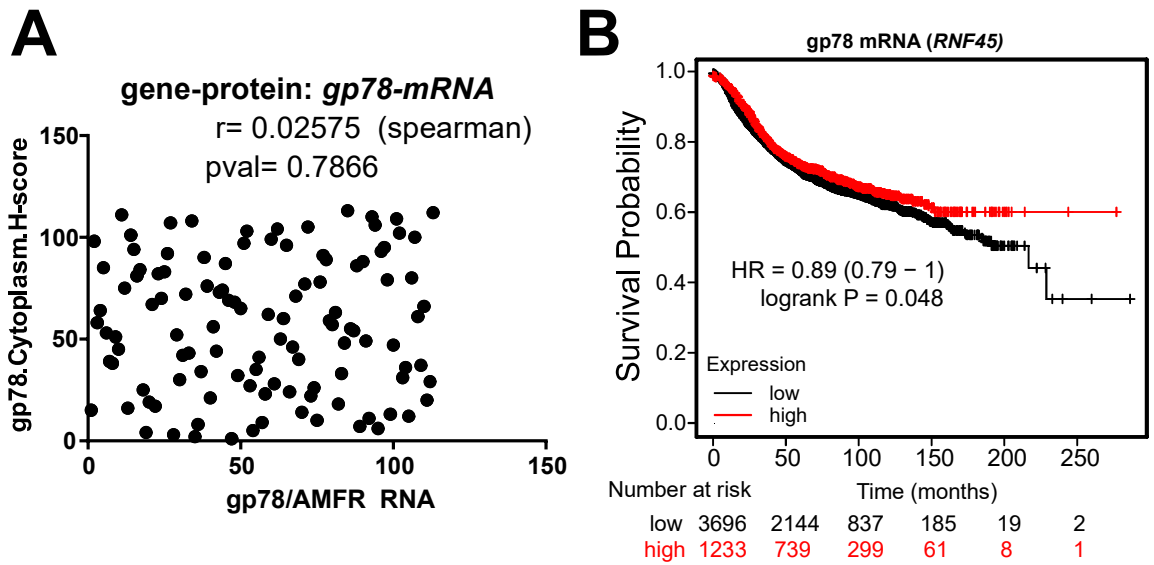
| Multivariate analysis: HR (All) | HR | CI (95%) lower | CI (95%) upper | p-value |
|---|---|---|---|---|
| AGE | 1.0264 | 1.0043 | 1.049 | **0.0192** |
| BMI | 0.9927 | 0.9684 | 1.018 | 0.5641 |
| RACE_(AA) | 1.0533 | 0.7206 | 1.539 | 0.7887 |
| Menopause_Status | 1.0184 | 0.5358 | 1.935 | 0.9557 |
| Subtype.bin_ LumB | 1.3584 | 0.7982 | 2.312 | 0.2589 |
| Subtype.bin_HER2+ | 2.296 | 0.9125 | 5.777 | 0.0775 |
| Subtype.bin_ TNBC | 2.772 | 1.1891 | 6.462 | **0.0182** |
| ER_subtype_ | 0.9989 | 0.447 | 2.233 | 0.9979 |
| Grade_2 | 1.1443 | 0.7067 | 1.853 | 0.5836 |
| Grade_3 | 1.462 | 0.7929 | 2.696 | 0.2237 |
| Node_Status_Yes | 2.1785 | 1.4824 | 3.201 | **7.37E-05** |
| gp78_Cyto_(High) | 0.9968 | 0.9935 | 1 | **0.0613** |
| | | | | |
| **Multivariate analysis: HR (EA)** | **HR** | **CI (95%) lower** | **CI (95%) upper** | **p-value** |
| AGE | 1.0227 | 0.9958 | 1.05 | 0.0991 |
| BMI | 0.9818 | 0.9487 | 1.016 | 0.2958 |
| Menopause_Status | 0.9548 | 0.3973 | 2.295 | 0.9177 |
| Subtype.bin_LumB | 0.9571 | 0.4469 | 2.05 | 0.9101 |
| Subtype.bin_HER2+ | 2.3411 | 1.0187 | 5.38 | **0.0451** |
| Subtype.bin_TNBC | 3.9597 | 2.1732 | 7.215 | **6.94E-06** |
| gp78_Cyto_(High) | 1.3309 | 0.6802 | 2.604 | 0.4039 |
| | | | | |
| **Multivariate analysis: HR (AA)** | **HR** | **CI (95%) lower** | **CI (95%) upper** | **p-value** |
| AGE | 1.0082 | 0.9799 | 1.037 | 0.5738 |
| BMI | 0.9908 | 0.9614 | 1.021 | 0.5452 |
| Menopause_Status | 1.3897 | 0.6046 | 3.194 | 0.4384 |
| Subtype.bin_LumB | 1.1653 | 0.6004 | 2.262 | 0.6512 |
| Subtype.bin_HER2+ | 1.8605 | 0.8062 | 4.294 | **0.1457** |
| Subtype.bin_TNBC | 0.9595 | 0.473 | 1.947 | **0.9089** |
| gp78_Cyto_(High) | 1.9961 | 1.1278 | 3.533 | **0.0177** |

| Multivariate analysis: HR (EA) | HR | CI (95%) lower | CI (95%) upper | p-value |
|---|---|---|---|---|
| AGE | 1.0248 | 0.9974 | 1.053 | 0.0762 |
| BMI | 0.9832 | 0.9508 | 1.017 | 0.3214 |
| Menopause_Status | 0.8929 | 0.3674 | 2.17 | 0.8025 |
| Subtype.bin_LumB | 0.9738 | 0.4465 | 2.124 | 0.9467 |
| Subtype.bin_HER2+ | 2.1747 | 0.8878 | 5.327 | 0.0892 |
| Subtype.bin_TNBC | 3.9022 | 2.0375 | 7.473 | **4.01E-05** |
| Grade_2 | 0.8202 | 0.4444 | 1.514 | 0.5262 |
| Grade_3 | 1.166 | 0.5348 | 2.542 | 0.6993 |
| gp78_Cyto (High) | 1.2385 | 0.6193 | 2.477 | 0.5453 |
| | | | | |
| **Multivariate analysis: HR (AA)** | **HR** | **CI (95%) lower** | **CI (95%) upper** | **p-value** |
| AGE | 1.0053 | 0.9768 | 1.035 | 0.7201 |
| BMI | 0.9931 | 0.9633 | 1.024 | 0.6587 |
| Menopause_Status | 1.5408 | 0.6628 | 3.582 | 0.3152 |
| Subtype.bin_LumB | 1.0842 | 0.5554 | 2.117 | 0.8127 |
| Subtype.bin_HER2+ | 1.4165 | 0.586 | 3.424 | 0.4394 |
| Subtype.bin_TNBC | 0.8016 | 0.378 | 1.7 | 0.5642 |
| Grade_2 | 1.986 | 0.9562 | 4.125 | 0.0658 |
| Grade_3 | 2.0083 | 0.8046 | 5.013 | 0.1352 |
| gp78_Cyto (High) | 1.8288 | 1.0267 | 3.258 | **0.0404** |

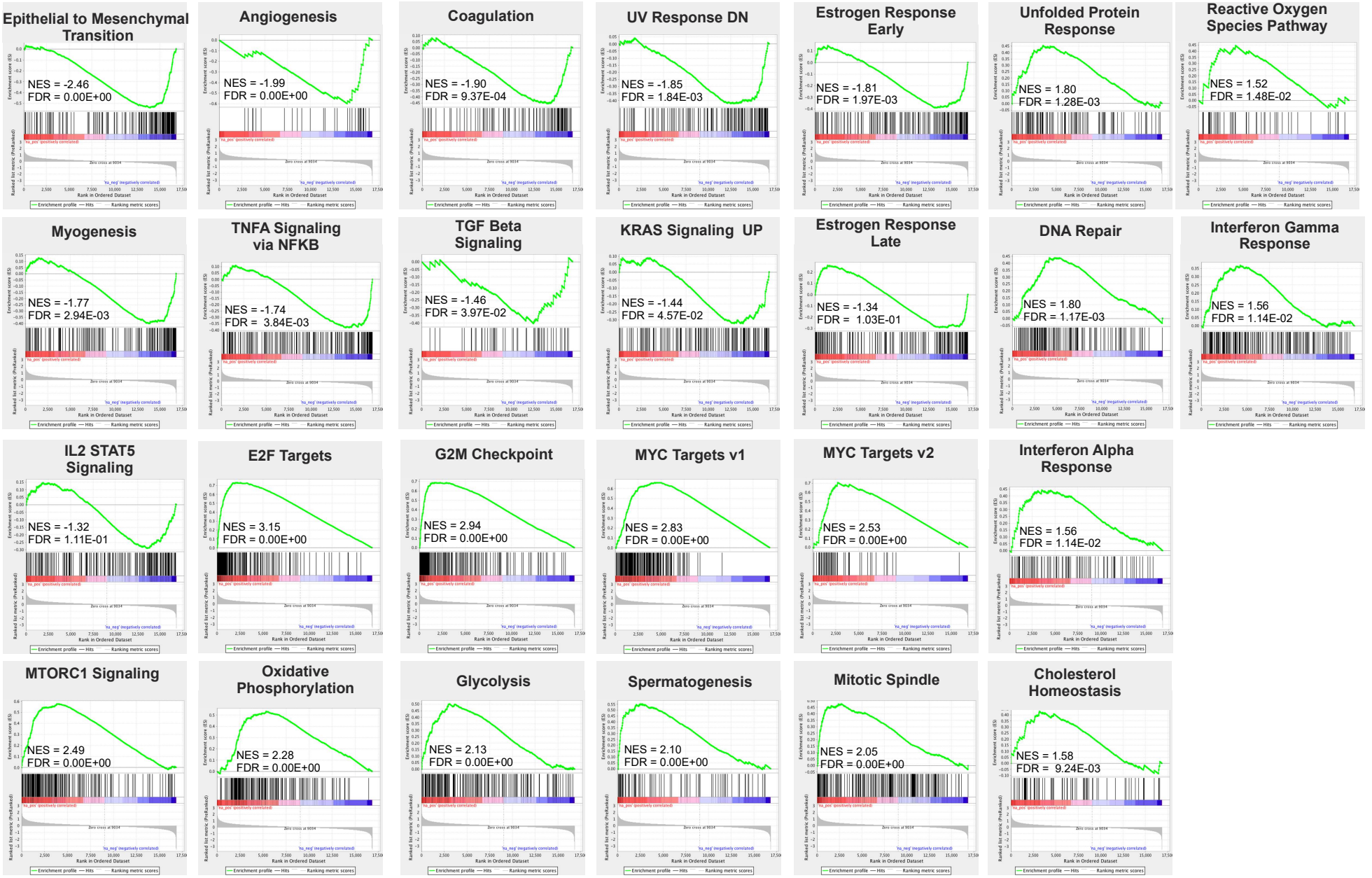
**Supplemental Table 1:** **(left, top)** Table showing multivariate analysis of the independent predictive value of gp78 protein levels for survival after adjusting for age, BMI, menopause status, subtype, ER status, grade, and lymph node status. **(left, middle).** Shown is the multivariate analysis of the association between gp78 and survival adjusted for age, BMI, menopause status, and subtype in women of European ancestry compared to **(left, bottom)** women of African ancestry. **(Right)** Multivariate analysis of the relationship between gp78 protein expression and survival after adjusting for age, BMI, menopause status, subtype, and grade comparing patients of European **(right, top)** versus African ancestry **(right, bottom).**

| Negatively regulated | | | | | |
|---|---|---|---|---|---|
| **NAME** | SIZE | ES | NES | NOM p-val | FDR q-val |
| HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION | 187 | -0.5422555 | -2.4593184 | 0 | 0 |
| HALLMARK_ANGIOGENESIS | 32 | -0.6005164 | -1.9944273 | 0 | 0 |
| HALLMARK_COAGULATION | 100 | -0.4565779 | -1.9019318 | 0 | 9.37E-04 |
| **HALLMARK_UV_RESPONSE_DN** | 141 | -0.4224794 | -1.8528675 | 0 | 0.0018427 |
| HALLMARK_ESTROGEN_RESPONSE_EARLY | 192 | -0.3925208 | -1.8076392 | 0 | 0.00197182 |
| HALLMARK_MYOGENESIS | 163 | -0.4013614 | -1.7727724 | 0 | 0.00294342 |
| **HALLMARK_TNFA_SIGNALING_VIA_NFKB** | 185 | -0.3829449 | -1.7420073 | 0 | 0.00383526 |
| HALLMARK_TGF_BETA_SIGNALING | 52 | -0.4041367 | -1.4640652 | 0.02356021 | 0.03968911 |
| HALLMARK_KRAS_SIGNALING_UP | 162 | -0.3229919 | -1.4377202 | 0 | 0.04565698 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 183 | -0.2956423 | -1.3355744 | 0.01587302 | 0.10309143 |
| HALLMARK_IL2_STAT5_SIGNALING | 188 | -0.2898708 | -1.3152194 | 0.015625 | 0.11083192 |
| **Positively regulated** | | | | | |
| **NAME** | SIZE | ES | NES | NOM p-val | FDR q-val |
| **HALLMARK_E2F_TARGETS** | 198 | 0.7348152 | 3.1534355 | 0 | 0 |
| **HALLMARK_G2M_CHECKPOINT** | 198 | 0.6890323 | 2.9352474 | 0 | 0 |
| HALLMARK_MYC_TARGETS_V1 | 197 | 0.6626929 | 2.8335598 | 0 | 0 |
| **HALLMARK_MYC_TARGETS_V2** | 58 | 0.7101932 | 2.5339458 | 0 | 0 |
| **HALLMARK_MTORC1_SIGNALING** | 198 | 0.57870287 | 2.491436 | 0 | 0 |
| **HALLMARK_OXIDATIVE_PHOSPHORYLATION** | 198 | 0.532552 | 2.2767758 | 0 | 0 |
| HALLMARK_GLYCOLYSIS | 185 | 0.5042823 | 2.1331122 | 0 | 0 |
| HALLMARK_SPERMATOGENESIS | 78 | 0.55520177 | 2.0961428 | 0 | 0 |
| HALLMARK_MITOTIC_SPINDLE | 198 | 0.47774455 | 2.049001 | 0 | 0 |
| **HALLMARK_UNFOLDED_PROTEIN_RESPONSE** | 110 | 0.45504516 | 1.8015443 | 0 | 0.00128385 |
| **HALLMARK_DNA_REPAIR** | 140 | 0.44054726 | 1.7955732 | 0 | 0.00116714 |
| HALLMARK_INTERFERON_ALPHA_RESPONSE | 89 | 0.44273165 | 1.7006303 | 0.0015949 | 0.00262745 |
| HALLMARK_CHOLESTEROL_HOMEOSTASIS | 72 | 0.42977247 | 1.5846494 | 0.01102362 | 0.00924402 |
| HALLMARK_INTERFERON_GAMMA_RESPONSE | 183 | 0.36937878 | 1.5571733 | 0.00144509 | 0.01139262 |
| **HALLMARK_REACTIVE_OXIGEN_SPECIES_PATHWAY** | 46 | 0.4461603 | 1.521564 | 0.01858108 | 0.0147807 |

**Supplemental Table 2:** Comparison of the GSEA normalized enrichment scores (NES) for patients stratified by gp78 protein. RED indicates gene sets also enriched significantly in the GSEA analysis of TCGA breast cancer patients stratified by Race (*J Clin Invest* 129, 2351-2356 (2019).




**Supplementary Figure 2:** (**A**) Correlation between gp78 protein expression by IHC and mRNA expression. r and p-value are shown for Spearman correlation. (**B**) Survival based on gp78 mRNA gene expression (generated from Győrffy B. *Computational and Structural Biotechnology Journal*, 2021, https://doi.org/10.1016/j.csbj.2021.07.014).




**Supplementary Figure 3:** Gene set enrichment analysis of RNA-seq data of ECU breast cancer patients stratified by high versus low gp78 protein levels.

A

| NHB (AA) Patients GSEA | | | | | |
|---|---|---|---|---|---|
| **Hallmark Geneset Name** | **SIZE** | **ES** | **NES** | **NOM p-val** | **FDR q-val** |
| E2F_TARGETS | 157.000 | 0.618 | 3.813 | <0.001 | <0.001 |
| G2M_CHECKPOINT | 133.000 | 0.624 | 3.733 | <0.001 | <0.001 |
| MITOTIC_SPINDLE | 80.000 | 0.503 | 2.733 | <0.001 | <0.001 |
| MTORC1_SIGNALING | 105.000 | 0.428 | 2.434 | <0.001 | <0.001 |
| MYC_TARGETS_V1 | 124.000 | 0.404 | 2.411 | <0.001 | <0.001 |
| GLYCOLYSIS | 70.000 | 0.460 | 2.395 | <0.001 | <0.001 |
| SPERMATOGENESIS | 35.000 | 0.516 | 2.268 | <0.001 | <0.001 |
| MYC_TARGETS_V2 | 41.000 | 0.446 | 2.081 | <0.001 | 0.001 |
| OXIDATIVE_PHOSPHORYLATION | 82.000 | 0.339 | 1.824 | <0.001 | 0.009 |
| ***CHOLESTEROL_HOMEOSTASIS*** | 28.000 | 0.429 | **1.759** | 0.007 | **0.014** |
| ***UNFOLDED_PROTEIN_RESPONSE*** | 48.000 | 0.353 | **1.677** | 0.007 | **0.025** |
| ***REACTIVE_OXIGEN_SPECIES_PATHWAY*** | 19.000 | 0.451 | **1.660** | 0.024 | **0.026** |

B

| NHW (EA) Patients GSEA | | | | | |
|---|---|---|---|---|---|
| **Hallmark Geneset Name** | **SIZE** | **ES** | **NES** | **NOM p-val** | **FDR q-val** |
| E2F_TARGETS | 111.000 | 0.470 | 2.749 | <0.001 | <0.001 |
| G2M_CHECKPOINT | 95.000 | 0.477 | 2.704 | <0.001 | <0.001 |
| ***INTERFERON_GAMMA_RESPONSE*** | 49.000 | 0.500 | **2.441** | <0.001 | **<0.001** |
| ***INTERFERON_ALPHA_RESPONSE*** | 35.000 | 0.542 | **2.421** | <0.001 | **<0.001** |
| SPERMATOGENESIS | 26.000 | 0.510 | 2.139 | <0.001 | 0.002 |
| MYC_TARGETS_V1 | 101.000 | 0.364 | 2.115 | <0.001 | 0.002 |
| MTORC1_SIGNALING | 82.000 | 0.377 | 2.052 | <0.001 | 0.003 |
| MITOTIC_SPINDLE | 57.000 | 0.373 | 1.891 | 0.006 | 0.014 |
| OXIDATIVE_PHOSPHORYLATION | 72.000 | 0.344 | 1.860 | 0.002 | 0.015 |
| GLYCOLYSIS | 51.000 | 0.376 | 1.849 | 0.003 | 0.014 |
| MYC_TARGETS_V2 | 25.000 | 0.415 | 1.682 | 0.015 | 0.047 |
| ***HEME_METABOLISM*** | 30.000 | 0.365 | **1.553** | 0.036 | **0.101** |

**Supplemental Table 3:** Comparison of the GSEA normalized enrichment (NES) scores for patients stratified by gp78 protein. NHB patients (**A**) and NHW patients (**B**). RED indicates gene sets exclusively enriched in AA patients compared to EA patients, and BLUE indicates genes exclusively enriched in EA patients compared to AA patients.

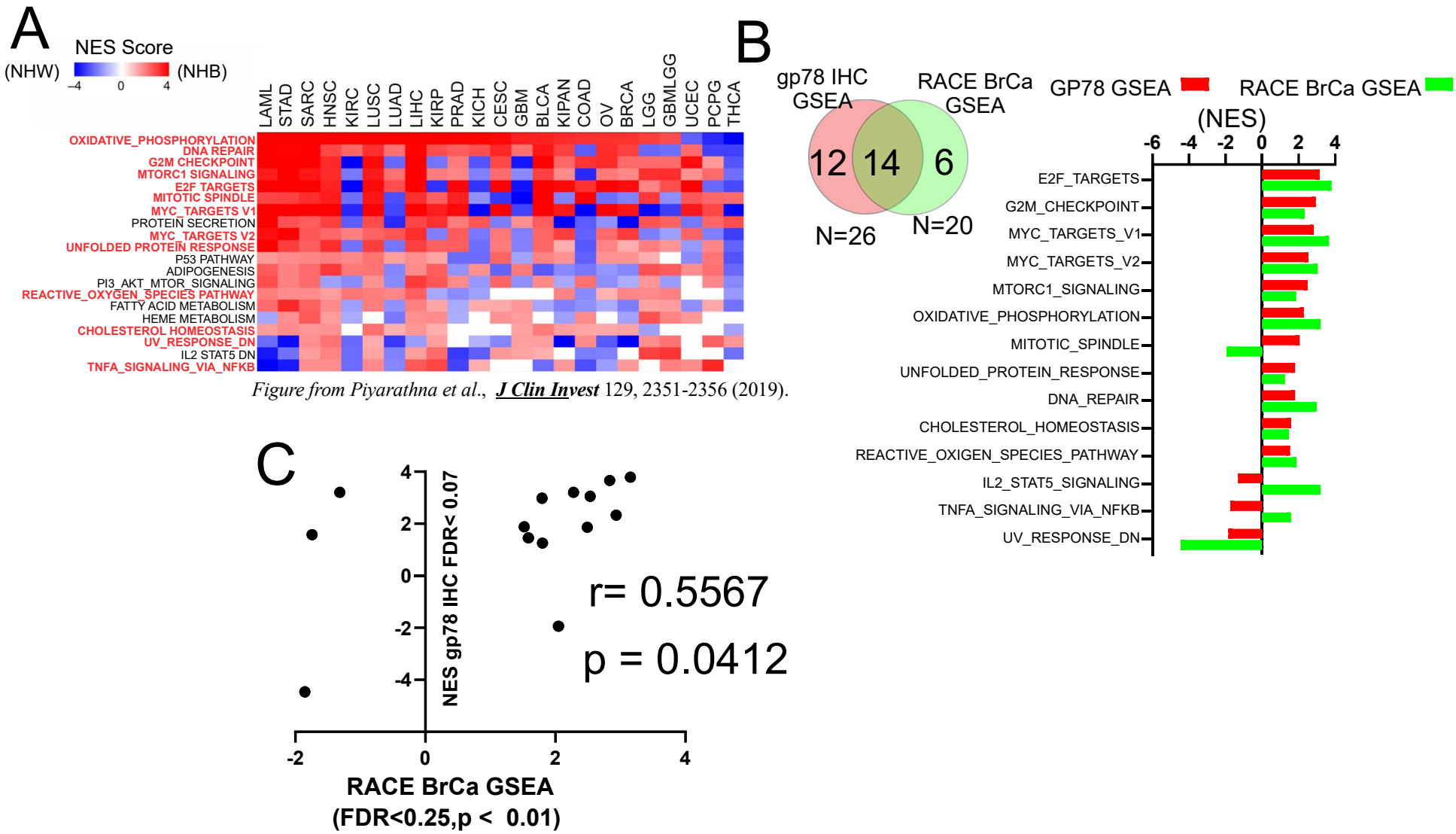
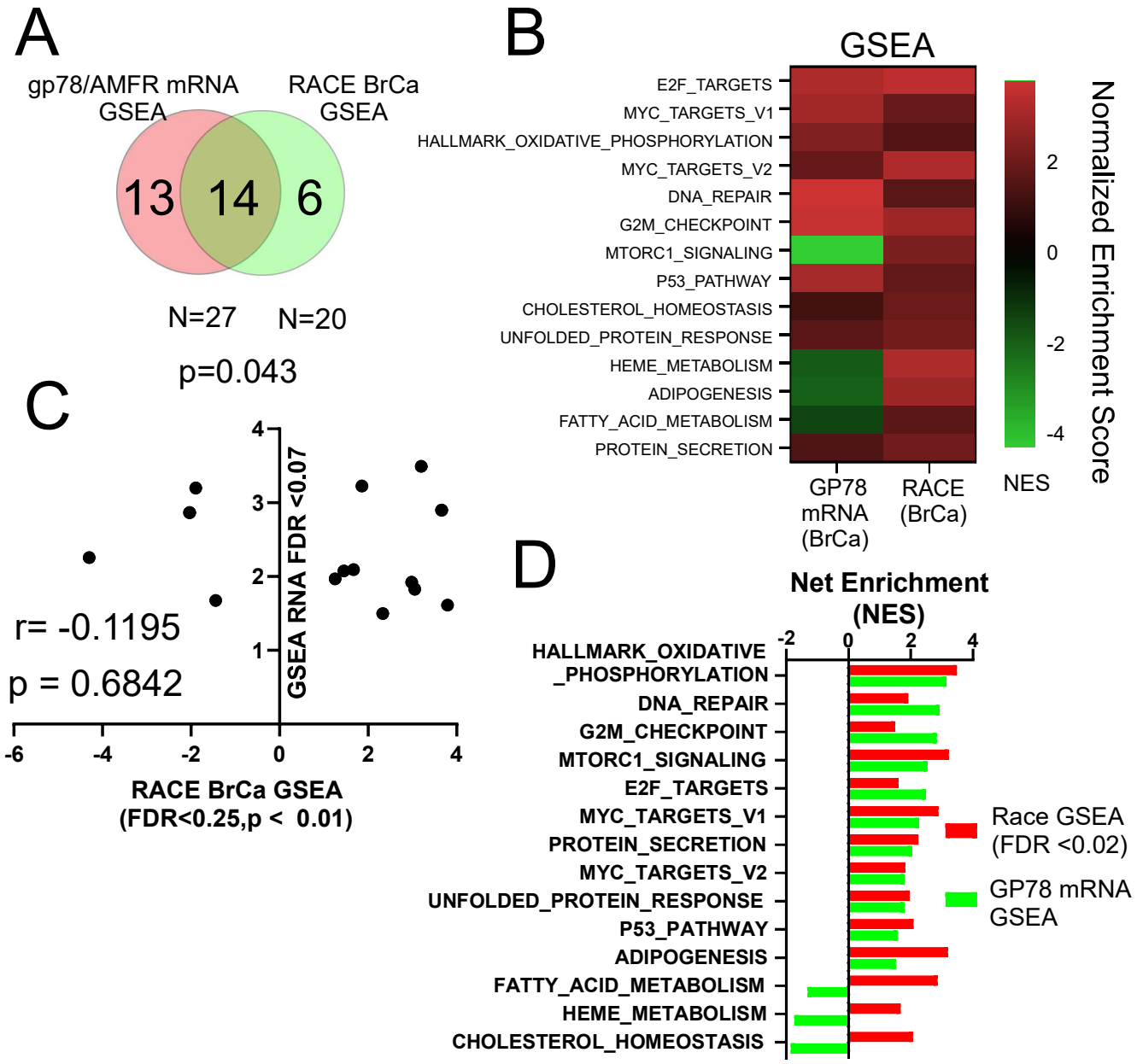
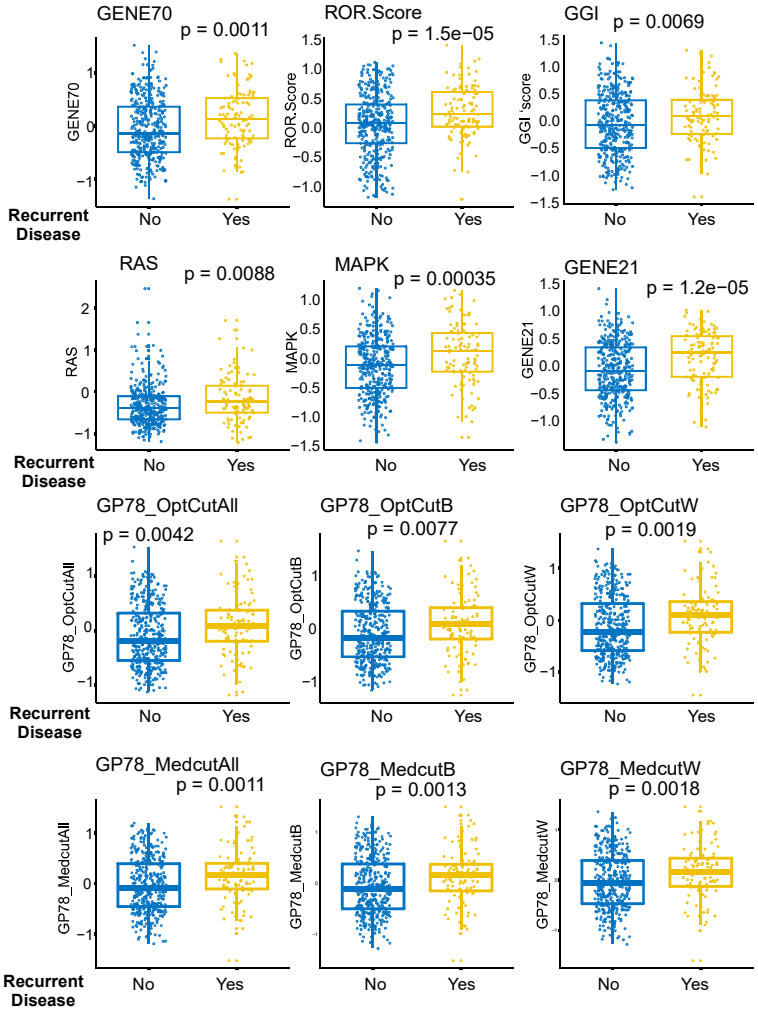



*Figure from Piyarathna et al.,* ***J Clin Invest*** 129, 2351-2356 (2019).

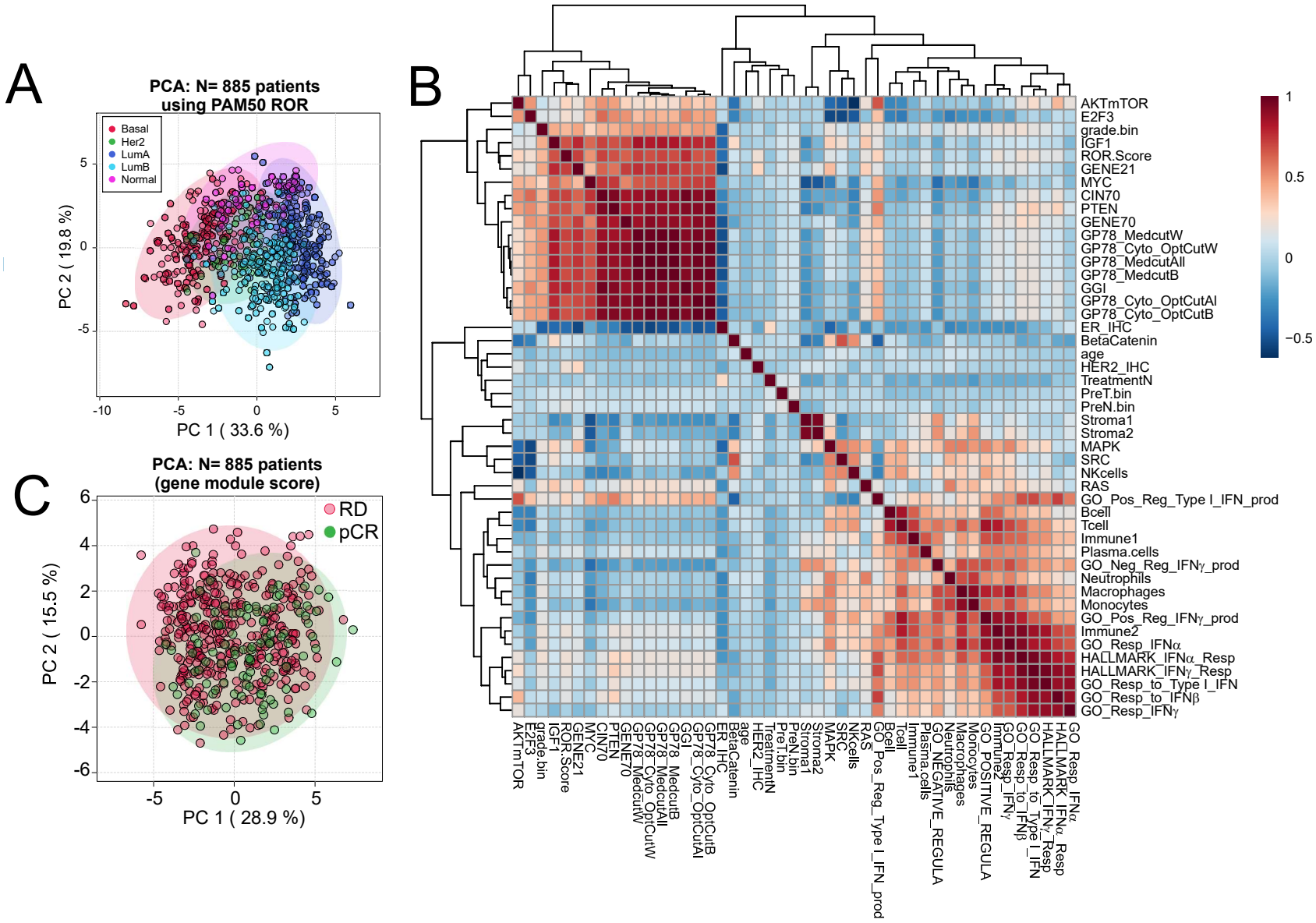
**Supplemental Figure 4:** Comparison of the GSEA normalized enrichment (NES) scores for patients stratified by gp78 IHC protein expression compared to the TCGA breast cancer patient tumors stratified by Race. (**A**) Heat map of normalized enrichment score of tumors stratified by race (J Clin Invest 129, 2351-2356 (2019). Gene sets in red indicated genes sets that are common to the TCGA breast cancer GSEA based on Race and the ECU breast cancer GSEA based on gp78 protein. (**B**) Venn diagram and histogram showing the overlap between gp78 protein GSEA and the TCGA breast cancer GSEA. (**C**) Spearman correlation analysis of NES derived from the TCGA breast cancer GSEA based on race and the ECU GSEA based on gp78 protein.



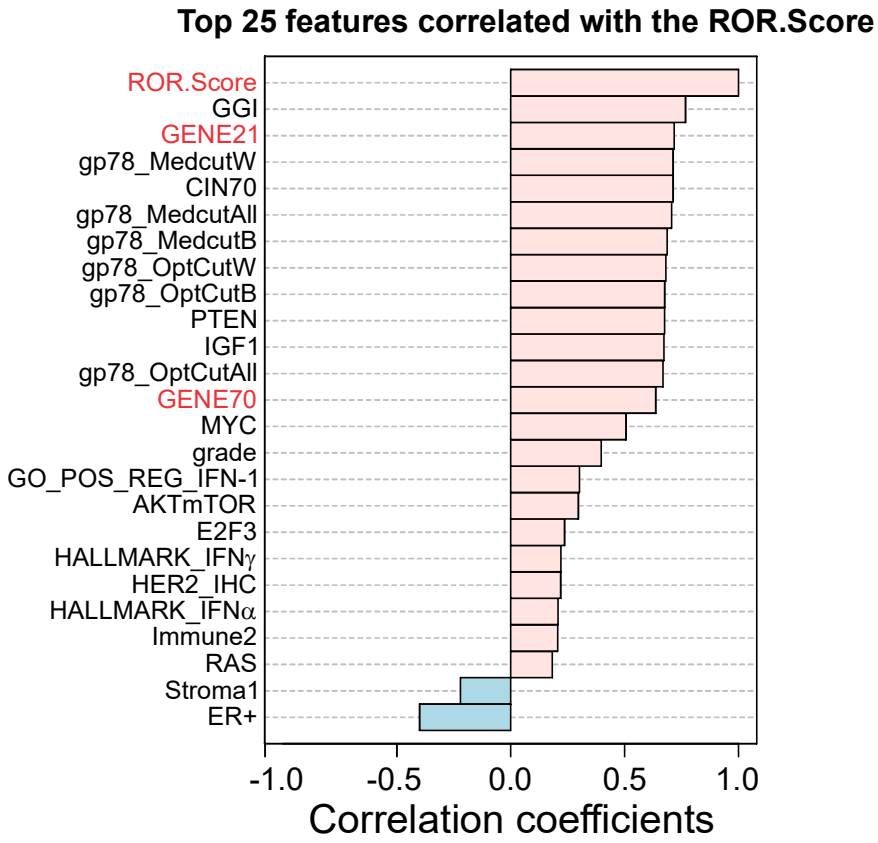

**Supplemental Figure 5:** Comparison of the GSEA normalized enrichment (NES) scores for patients stratified by gp78 RNA expression compared to RNA-seq data from TCGA breast cancer patient tumors stratified by Race. Venn diagram showing the overlap between GSEA of ECU RNA-seq data stratified by gp78 mRNA compared to TCGA breast cancer RNA-seq data stratified by Race (**A**). Heat map of TCGA and ECU breast cancer GSEA stratified by gp78 mRNA (**B**). Spearman correlation analysis of GSEA NES scores from TCGA breast cancer RNA-seq data stratified by Race and the ECU RNA-seq data stratified by gp78 mRNA (**C**). Histogram comparison of GSEA NES comparing TCGA RNA-seq data stratified by race and ECU RNA-seq data stratified by gp78 mRNA.



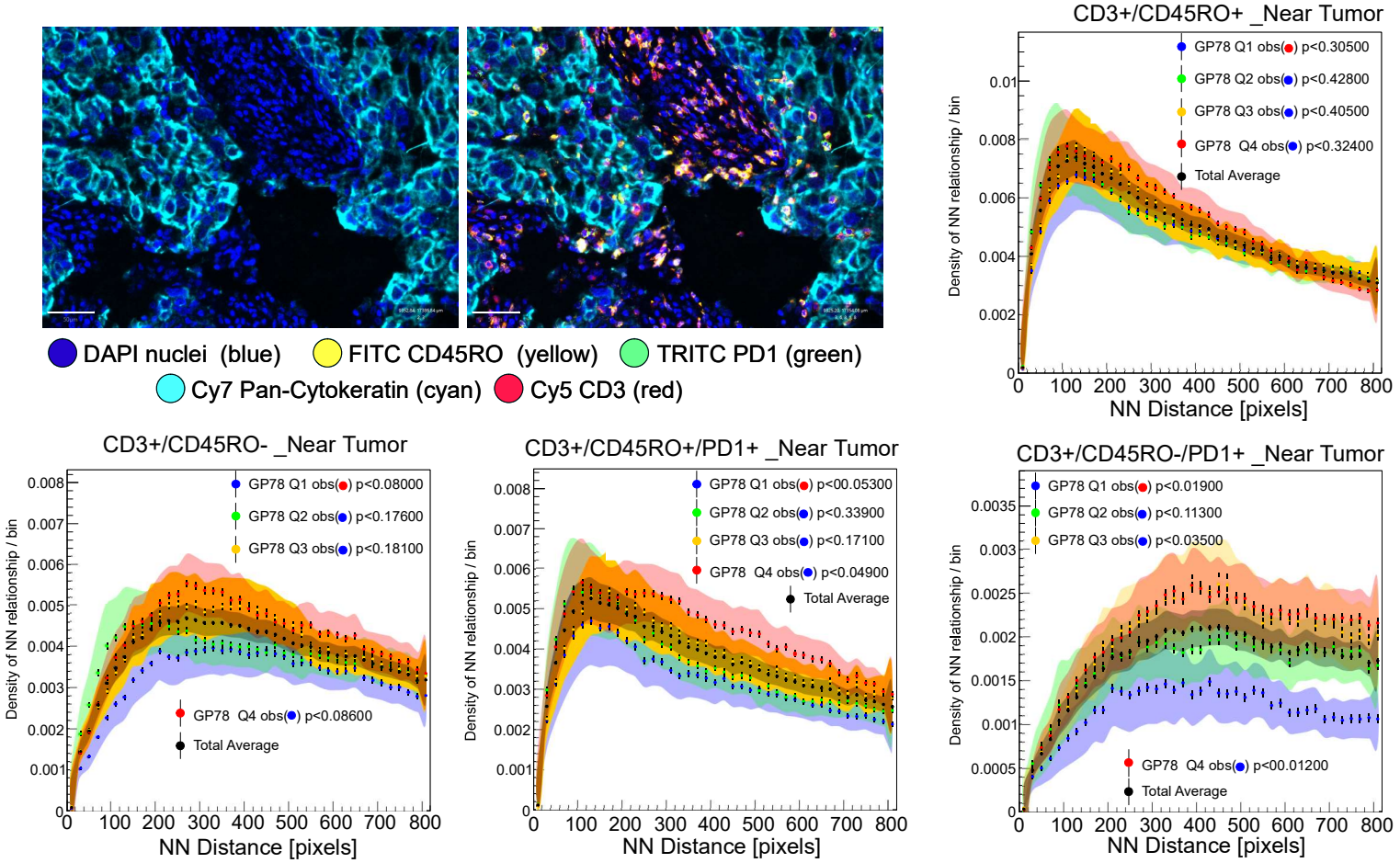

**Supplementary Figure 6:** gp78-derived gene module scores in patients with and without recurrent disease compared to previously established gene signatures scores (*JCO 30 (16):1966-2004* (2012)).



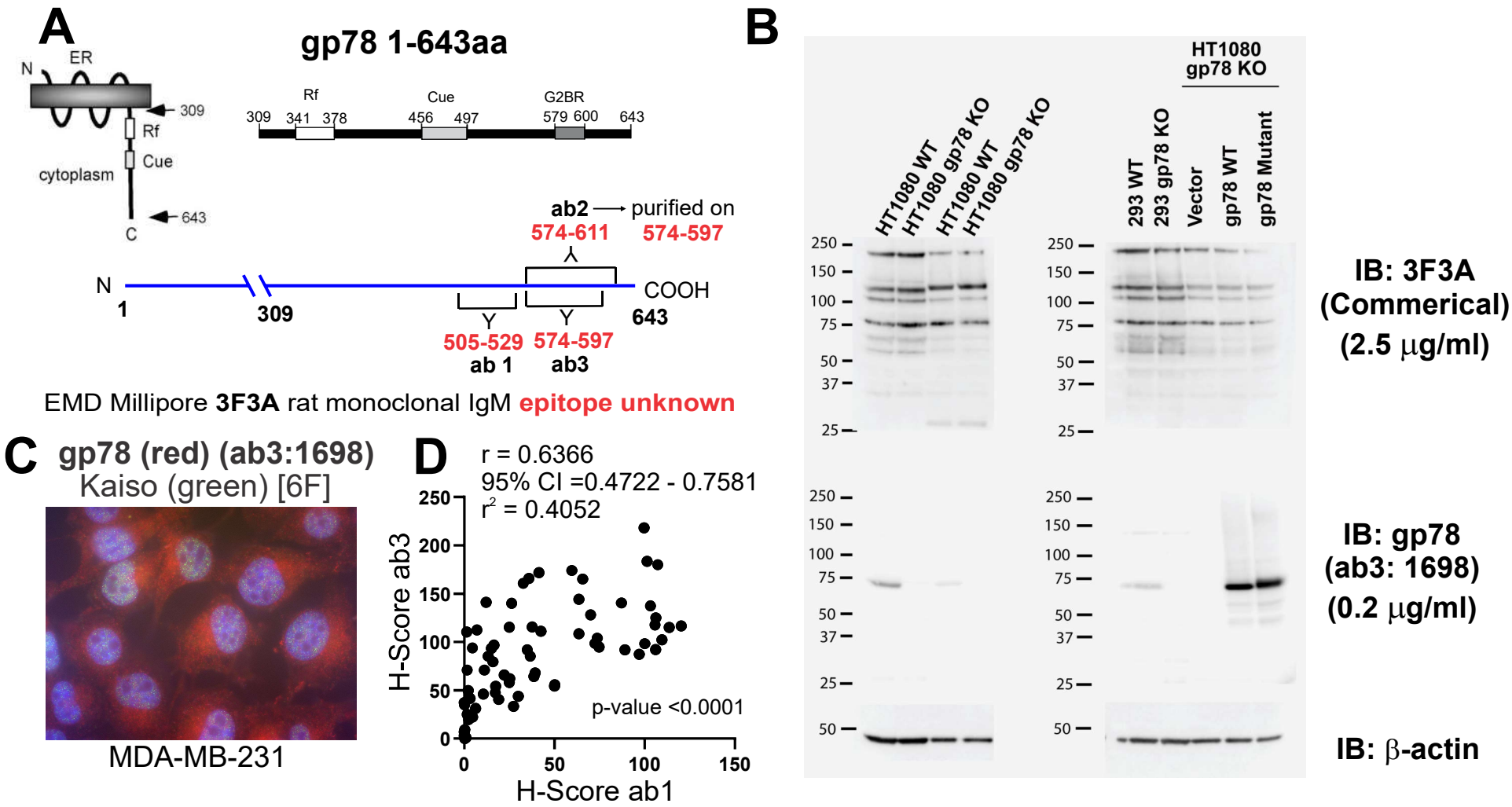

**Supplementary Figure 7**: gp78-derived gene module scores in patients with and without recurrent disease compared to previously established gene signatures scores (*JCO 30 (16):1966-2004* (2012)). (**A**) PCA analysis of patients using the PAM50 ROR gene signature. (**B**) Hierarchical clustering of correlation coefficients of gp78-derived scores and those previously described (JCO 30 (16):1966-2004 (2012). (**C**) PCA separation of all gene modules scores of patients with a complete pathological response (pCR) compared to residual disease (RD) (data taken from (*JCO 30 (16):1966-2004* (2012)).



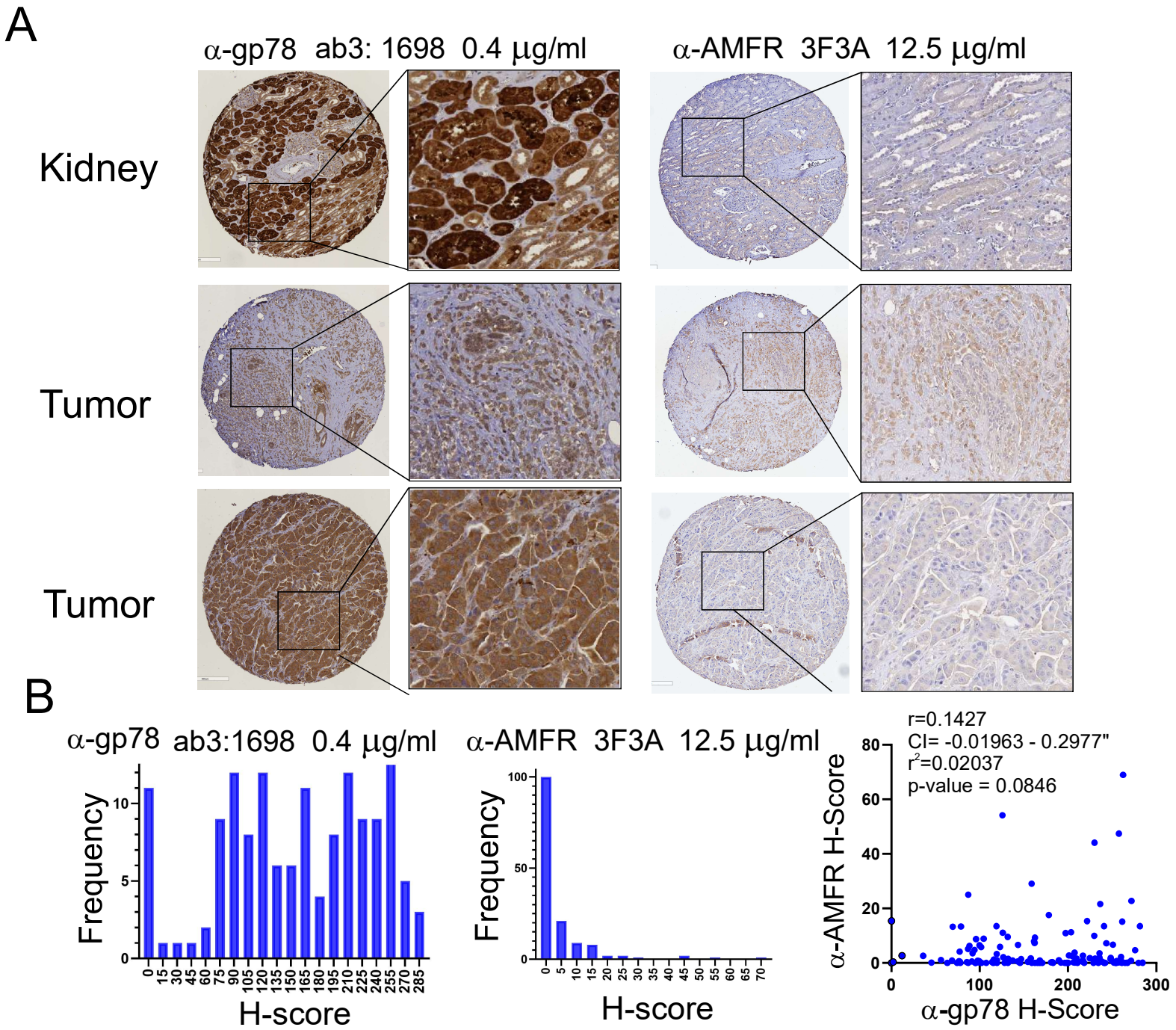

**Supplementary Figure 8:** gp78-derived gene module scores correlation with the ROR.score. gp78-derived module scores show a significant correlation with ROR (Prosignia), GENE21 (Oncotype), and GENE70 (Mammaprint) gene signatures.



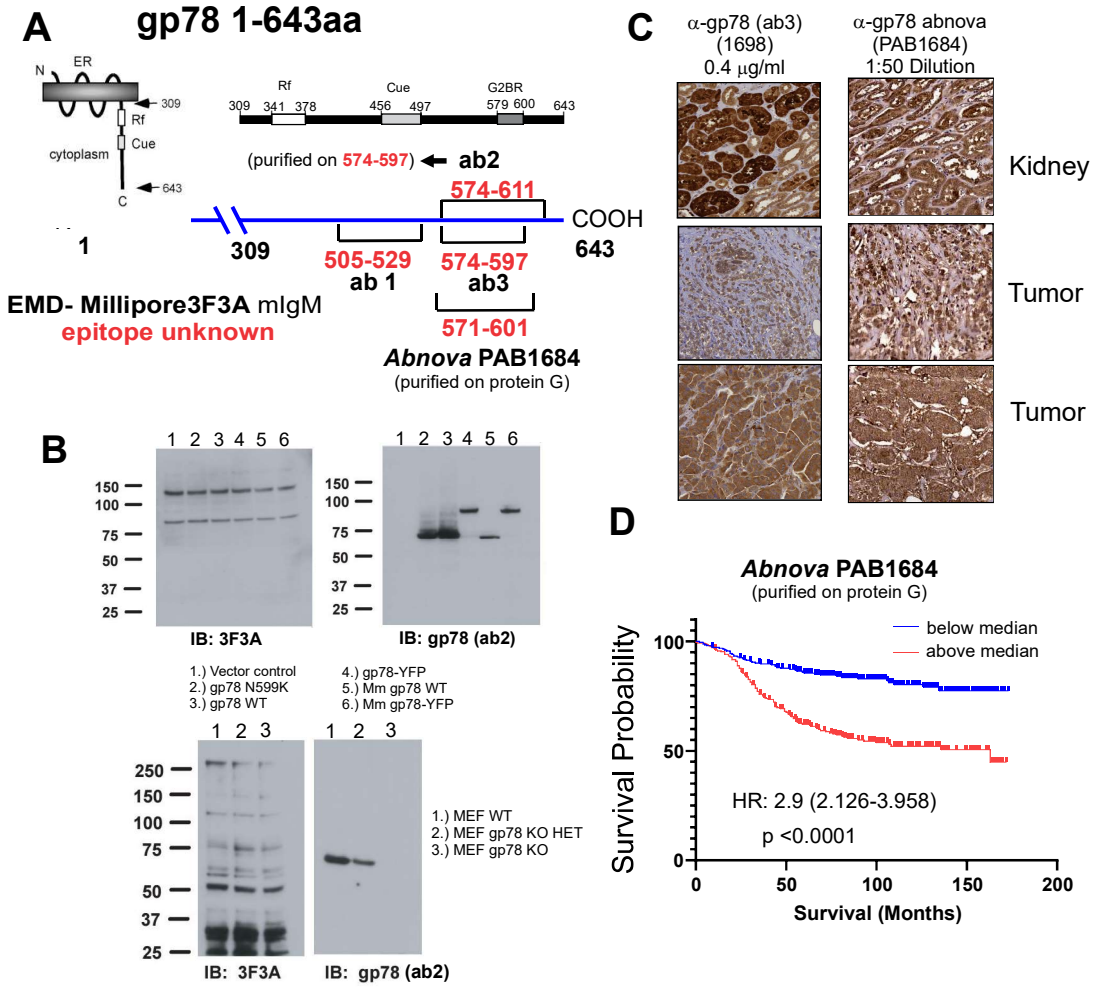

**Supplementary Figure 9:** Proximity analysis of the association between gp78 protein expression and immune-modulatory features in the tumor microenvironment using markers for activated memory T-cells (CD3, CD45RO) and immune exhaustion (PD-1). Data show there is no significant correlation between gp78 protein levels and T-cell exhaustion in proximity to the tumor.



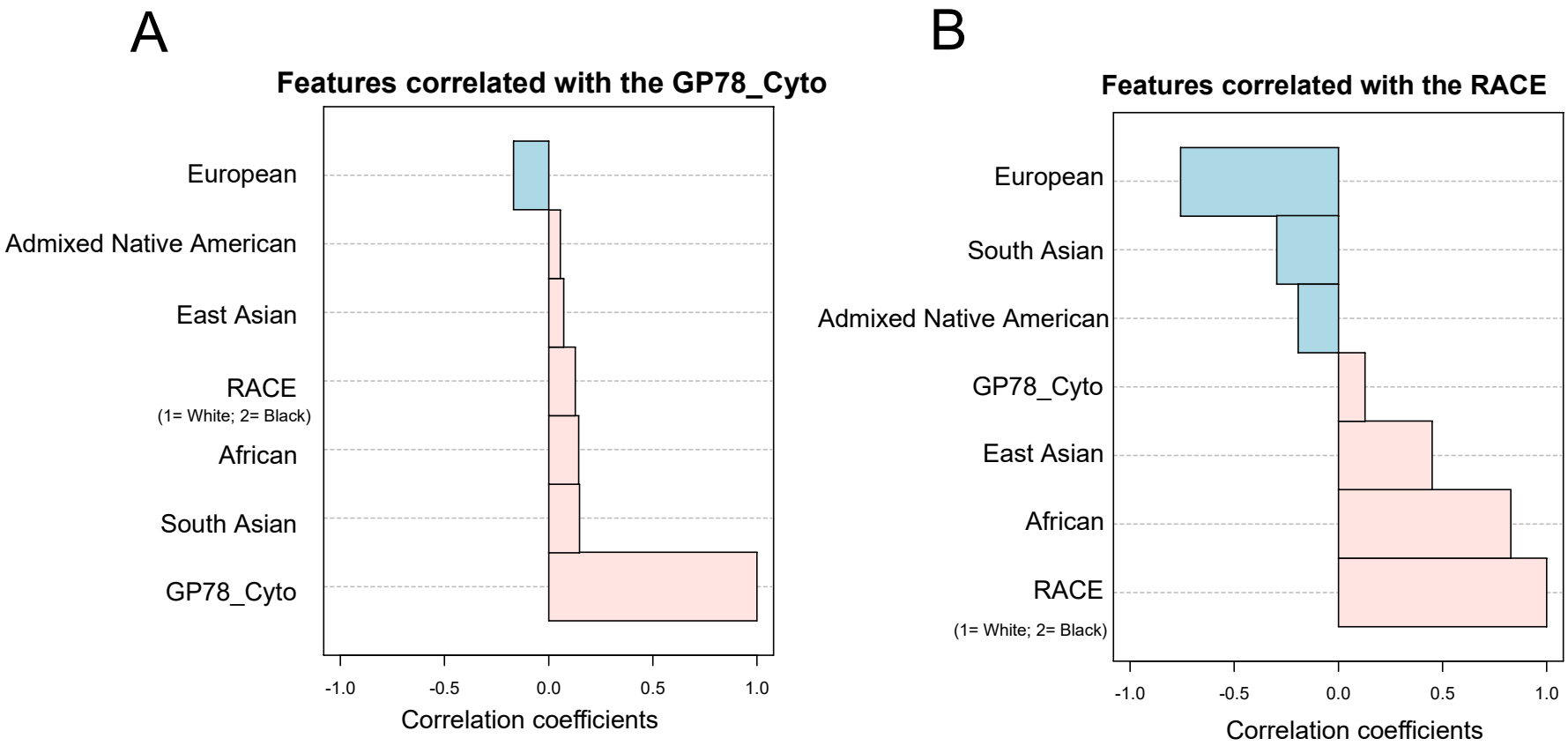

**Supplementary Figure 10:** (**A**) Schematic diagram of endoplasmic reticulum-resident gp78 showing the cytoplasmic domains. (below) is a schematic show location of peptides used as immunogens for each antibody **note that gp78 epitopes reactive with 3F3A are unknown** (**B**). Lysates from HT1080 parental and gp78 KO cells (left) and gp78KO cells rescued by wildtype and mutant gp78 were resolved by SDS-PAGE and immunoblotted with 3F3A monoclonal antibody (5 g/mL) (top). The membrane was then reblotted with gp78 ab3 (0.2 g/mL) (Middle) and then (Bottom) reblotted for actin as a loading control. (bottom). (**C**) Immunofluorescence using gp78 ab3 (1:1000 ) (RED) on MDA-MB-231 cells grown in culture. Blue Dapi, Green Kaiso antibody. (**D**) Correlation between IHC gp78 scores using a previously published antibody (Ab1; PMID: 16407162) compared to Ab3. Spearman R is shown.




**Supplementary Figure 11:** (**A**) Direct side-by-side quantitative comparison of reactivity of. anti-gp78 Ab3 to 3F3A on normal tissue and tumor. (**B**) Quantitative assessment of gp78 abundance comparing Ab3 with 3F3A, including correlation of scores from a patient TMA.




**Supplementary Figure 12:** (**A**) Schematic diagram of endoplasmic reticulum-resident gp78 showing the cytoplasmic domains. (below) is a schematic show location of peptides used as immunogens for each antibody **note that gp78 epitopes reactive with 3F3A are unknown** (**B**) Upper Panel: (Left) Lysates from HEK293 cells transfected with the indicated plasmids were resolved by SDS-PAGE and immunoblotted with 5 ug/ml 3F3A monoclonal antibody. N599K eliminates the putative N-glycosylation site but does not result in any apparent mobility shift. (Right) A replicate membrane was immunoblotted with gp78 ab2 (PMID:18037895 (0.2 ug/ml). Lower Panel: (left) Lysates from wild-type (WT; gp78+/+), heterozygous (HET; gp78+/-) and knockout (KO; gp78-/-) primary mouse embryonic fibroblasts (MEFs) were resolved by SDS-PAGE and immunoblotted with 3F3A monoclonal antibody. (Right) A replicate membrane was immunoblotted with gp78 ab2 (0.2 g/mL). (**C**)IHC profiling of kidney and tumor comparing Ab3 and commercial antibody Abnova PAB1684. **note high Abnova PAB1684 background** (**D**) Survival curve showing that that high gp78 expression based on Abnova PAB1684 predicts poor breast cancer survival.




**Supplementary Figure 13:** (**A**) Correlation between genetic ancestry, race and gp78 protein scores. (**B**) Correlation between Race (white vs Black) and genetic ancestry and gp78 protein scores. RACE= self-identified Race.