**Table S1.** Clinicopathologic characteristics of breast cancer in the TCGA dataset

| Characteristic | TCGA | | |
|---|---|---|---|
| | RT (n=540) | NRT (n=406) | *P* value |
| Age | | | |
| <60 | 305 (56.48%) | 203 (50%) | 0.048 |
| ≥60 | 235 (43.52%) | 203 (50%) | |
| Histological type | | | |
| Lobular Carcinoma | 110 (20.37%) | 79 (19.46%) | 0.218 |
| Ductal Carcinoma | 387 (71.67%) | 281 (69.21%) | |
| Mixed | 16 (2.96%) | 11 (2.71%) | |
| Others | 27 (5%) | 34 (8.37%) | |
| NA | 0 | 1 (0.25%) | |
| Pathological stage | | | |
| I/II | 366 (67.78%) | 329 (81.03%) | <0.001 |
| III/IV | 165 (30.56%) | 67 (16.5%) | |
| NA | 9 (1.67%) | 10 (2.46%) | |
| ER | | | |
| ER- | 111 (20.56%) | 91 (22.41%) | 0.504 |
| ER+ | 406 (75.19%) | 299 (73.65%) | |
| NA | 23 (4.26%) | 16 (3.94%) | |
| PR | | | |
| PR- | 167 (30.93%) | 125 (30.79%) | 0.978 |
| PR+ | 350 (64.81%) | 263 (64.78%) | |
| NA | 23 (4.26%) | 18 (4.43%) | |
| HER2 | | | |
| HER2- | 280 (51.85%) | 197 (48.52%) | 0.141 |
| HER2+/- | 66 (12.22%) | 68 (16.75%) | |
| HER2+ | 105 (19.44%) | 76 (18.72%) | |
| NA | 89 (16.48%) | 65 (16.01%) | |
| Chemotherapy | | | |
| No | 26 (4.81%) | 62 (15.27%) | <0.001 |
| Yes | 486 (90%) | 282 (69.46%) | |
| NA | 28 (5.19%) | 62 (15.27%) | |
| Status | | | |
| alive | 491 (90.93%) | 348 (85.71%) | 0.012 |
| death | 49 (9.07%) | 58 (14.29%) | |
| SurvTime (month)* | 32.49 (18.61, 63.25) | 23.98 (13.47, 52.13) | <0.001 |

*P50(P25, P75); RT, radiotherapy; NRT, non-radiotherapy; NA, data not available; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

**Table S2.** Clinicopathologic characteristics of breast cancer in the METABRIC dataset

| Characteristic | METABRIC | | |
|---|---|---|---|
| | RT (n=1137) | NRT (n=764) | *P* value |
| Age | | | |
| <60 | 555 (48.81%) | 285 (37.3%) | <0.001 |
| ≥60 | 582 (51.19%) | 479 (62.7%) | |
| Histological type | | | |
| Lobular Carcinoma | 75 (6.6%) | 67 (8.77%) | 0.144 |
| Ductal Carcinoma | 885 (77.84%) | 566 (74.08%) | |
| Mixed | 115 (10.11%) | 92 (12.04%) | |
| Others | 53 (4.66%) | 33 (4.32%) | |

| | | | |
|---|---|---|---|
| NA | 9 (0.79%) | 6 (0.79%) | |
| Grade | | | |
| I | 82 (7.21%) | 82 (10.73%) | <0.001 |
| II | 402 (35.36%) | 338 (44.24%) | |
| III | 627 (55.15%) | 299 (39.14%) | |
| NA | 26 (2.29%) | 45 (5.89%) | |
| ER | | | |
| ER- | 305 (26.82%) | 138 (18.06%) | <0.001 |
| ER+ | 832 (73.18%) | 626 (81.94%) | |
| PR | | | |
| PR- | 562 (49.43%) | 331 (43.32%) | 0.009 |
| PR+ | 575 (50.57%) | 433 (56.68%) | |
| HER2 | | | |
| HER2- | 990 (87.07%) | 675 (88.35%) | 0.407 |
| HER2+ | 147 (12.93%) | 89 (11.65%) | |
| Chemotherapy | | | |
| No | 814 (71.59%) | 691 (90.45%) | <0.001 |
| Yes | 323 (28.41%) | 73 (9.55%) | |
| Status | | | |
| alive | 530 (46.61%) | 269 (35.21%) | <0.001 |
| death | 607 (53.39%) | 495 (64.79%) | |
| SurvTime (month)* | 116.63 (61.33, 182.93) | 114.28 (60.89, 186.88) | 0.818 |

*P50(P25, P75); RT, radiotherapy; NRT, non-radiotherapy; NA, data not available; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

**Table S3.** Clinicopathologic characteristics of breast cancer in the E-TABM-158 dataset

| Characteristic | E-TABM-158 | | |
|---|---|---|---|
| | RT (n=59) | NRT (n=56) | *P* value |
| Age | | | |
| <60 | 42 (71.19%) | 36 (64.29%) | 0.429 |
| ≥60 | 17 (28.81%) | 20 (35.71%) | |
| Pathological stage | | | |
| I/II | 48 (81.36%) | 45 (80.36%) | 0.936 |
| III/IV | 10 (16.95%) | 9 (16.07%) | |
| NA | 1 (1.69%) | 2 (3.57%) | |
| ER | | | |
| ER- | 24 (40.68%) | 19 (33.93%) | 0.455 |
| ER+ | 35 (59.32%) | 37 (66.07%) | |
| PR | | | |
| PR- | 26 (44.07%) | 25 (44.64%) | 0.984 |
| PR+ | 32 (54.24%) | 31 (55.36%) | |
| NA | 1 (1.69%) | 0 | |
| Chemotherapy | | | |
| No | 25 (42.37%) | 29 (51.79%) | 0.312 |
| Yes | 34 (57.63%) | 27 (48.21%) | |
| DSS | | | |
| alive | 44 (74.58%) | 44 (78.57%) | 0.613 |
| death | 15 (25.42%) | 12 (21.43%) | |
| SurvTime (month)* | 81.12 (45.18, 117.90) | 72.60 (36.06, 108.84) | 0.339 |

*P50(P25, P75); RT, radiotherapy; NRT, non-radiotherapy; NA, data not available; ER, estrogen receptor; PR, progesterone receptor; DSS, disease-specific survival.

**Table S4.** Clinicopathologic characteristics of breast cancer in the GSE103746 dataset

| Characteristic | GSE103746 | | |
|---|---|---|---|
| | RT (n=118) | NRT (n=54) | *P* value |
| ER | | | |
| ER- | 38 (32.20%) | 12 (22.22%) | 0.181 |
| ER+ | 80 (67.80%) | 42 (77.78%) | |
| NA | | | |
| Reference | | | |
| no | 68 (57.63%) | 36 (66.67%) | 0.261 |
| yes | 50 (42.37%) | 18 (33.33%) | |
| Follow-up time (month)* | 104.89 (46.46, 166.07) | 132.44 (61.60, 180.70) | 0.373 |

*P50(P25, P75); RT, radiotherapy; NRT, non-radiotherapy.

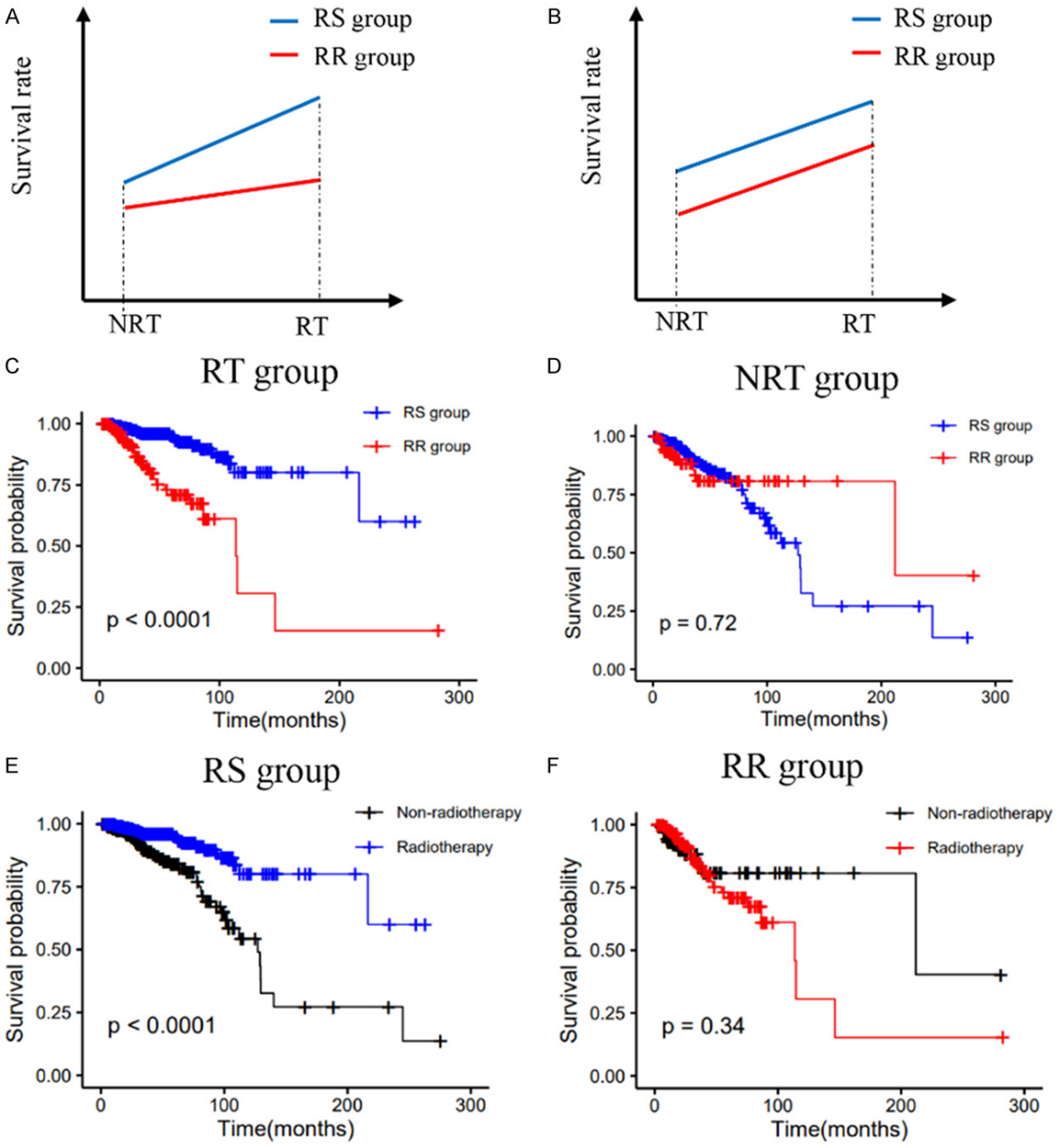


**Figure S1.** Definition of radiosensitivity and radiosensitivity gene signature.

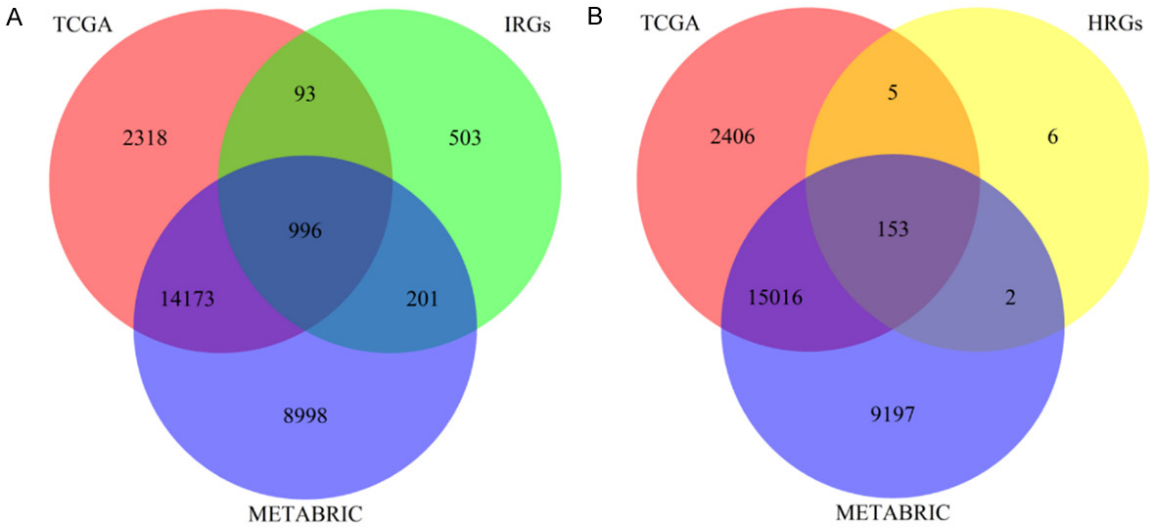


**Figure S2.** Venn diagram. The common immune-related genes (A) and hypoxia-related genes; (B) in the TCGA dataset, METABRIC datasets.

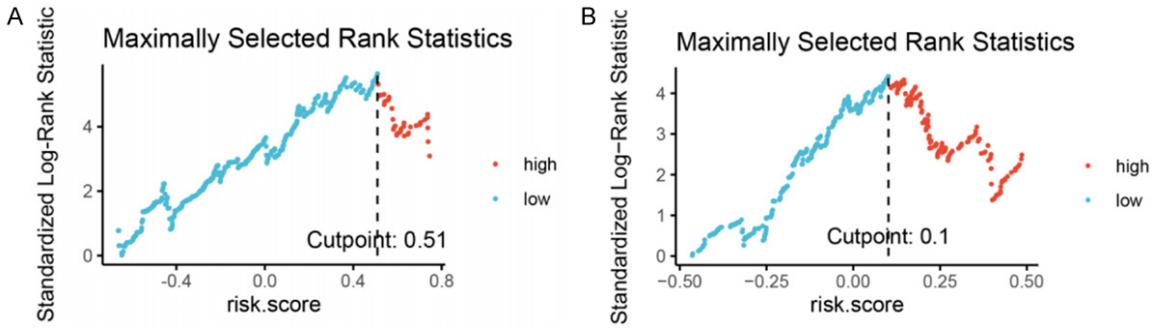


**Figure S3.** The optional cutoff values were determined by maximally selected rank statistics. A. Immune signature; B. Hypoxia signature.

**Table S5.** Univariate Cox regression analysis of radiotherapy and non-radiotherapy patients in the TCGA dataset

| Gene names | Radiotherapy for all patients | | Non-radiotherapy for all patients | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| IRGs | | | | |
| ACVRL1 | 1.371 (1.139-1.649) | 0.001 | 0.913 (0.679-1.226) | 0.543 |
| ADM | 1.277 (1.115-1.462) | <0.001 | 1.193 (0.835-1.703) | 0.332 |
| ADRM1 | 1.225 (1.060-1.417) | 0.006 | 1.146 (0.84-1.562) | 0.39 |
| AIMP1 | 1.099 (1.034-1.169) | 0.003 | 1.144 (0.415-3.155) | 0.795 |
| AKT1 | 1.267 (1.020-1.573) | 0.033 | 0.995 (0.754-1.314) | 0.973 |
| ANGPTL6 | 1.231 (1.035-1.463) | 0.019 | 1.081 (0.779-1.501) | 0.64 |
| ARRB1 | 1.336 (1.041-1.715) | 0.023 | 0.837 (0.479-1.464) | 0.533 |
| BMP1 | 1.250 (1.121-1.395) | <0.001 | 1.012 (0.658-1.555) | 0.957 |
| BMPR1A | 0.650 (0.457-0.924) | 0.016 | 0.949 (0.735-1.227) | 0.69 |
| BRAF | 0.449 (0.277-0.729) | 0.001 | 0.978 (0.734-1.304) | 0.88 |
| CBL | 0.723 (0.523-0.999) | 0.049 | 1.163 (0.854-1.585) | 0.337 |
| CCL26 | 1.359 (1.051-1.759) | 0.019 | 0.893 (0.473-1.687) | 0.727 |
| CD14 | 1.216 (1.089-1.357) | <0.001 | 0.996 (0.738-1.343) | 0.978 |
| CD320 | 1.199 (1.003-1.432) | 0.046 | 0.996 (0.733-1.354) | 0.98 |

| | | | | |
|---|---|---|---|---|
| CD81 | 1.368 (1.136-1.646) | 0.001 | 0.984 (0.774-1.251) | 0.895 |
| CMKLR1 | 1.288 (1.045-1.587) | 0.018 | 0.77 (0.506-1.171) | 0.221 |
| CMTM6 | 0.625 (0.426-0.916) | 0.016 | 0.808 (0.621-1.053) | 0.115 |
| CXCL1 | 1.353 (1.008-1.816) | 0.044 | 0.391 (0.126-1.215) | 0.105 |
| CXCL16 | 0.559 (0.348-0.897) | 0.016 | 0.893 (0.66-1.21) | 0.466 |
| DLL4 | 1.319 (1.105-1.576) | 0.002 | 1.081 (0.838-1.393) | 0.55 |
| EDN2 | 1.335 (1.077-1.655) | 0.008 | 0.922 (0.705-1.207) | 0.556 |
| ENG | 1.383 (1.136-1.683) | 0.001 | 0.825 (0.595-1.145) | 0.25 |
| ESRRA | 1.271 (1.001-1.612) | 0.049 | 1.262 (0.968-1.644) | 0.085 |
| F2RL1 | 1.293 (1.050-1.593) | 0.016 | 1.103 (0.869-1.399) | 0.42 |
| FAM3D | 1.200 (1.088-1.323) | <0.001 | 0.806 (0.432-1.503) | 0.497 |
| FCGRT | 1.263 (1.015-1.571) | 0.036 | 0.941 (0.703-1.26) | 0.685 |
| FIGNL2 | 1.359 (1.117-1.654) | 0.002 | 0.982 (0.751-1.284) | 0.895 |
| FLT4 | 1.235 (1.024-1.490) | 0.027 | 0.834 (0.589-1.182) | 0.308 |
| GDF11 | 1.283 (1.040-1.582) | 0.02 | 0.924 (0.666-1.282) | 0.637 |
| GDF3 | 1.213 (1.007-1.462) | 0.042 | 1.185 (0.871-1.612) | 0.279 |
| GFAP | 1.257 (1.080-1.462) | 0.003 | 0.689 (0.355-1.338) | 0.271 |
| GRN | 1.216 (1.014-1.458) | 0.035 | 1.084 (0.792-1.482) | 0.614 |
| HRAS | 1.249 (1.000-1.559) | 0.05 | 0.932 (0.652-1.333) | 0.701 |
| IL1A | 1.197 (1.099-1.303) | <0.001 | 0.378 (0.052-2.767) | 0.338 |
| IL31RA | 1.240 (1.092-1.406) | 0.001 | 1.135 (0.816-1.577) | 0.452 |
| KLRC2 | 0.208 (0.047-0.920) | 0.039 | 1.09 (0.876-1.355) | 0.44 |
| KLRC3 | 0.118 (0.021-0.646) | 0.014 | 1.018 (0.892-1.161) | 0.793 |
| LGR4 | 1.226 (1.001-1.501) | 0.049 | 0.876 (0.641-1.197) | 0.405 |
| LMBR1L | 1.371 (1.053-1.785) | 0.019 | 0.999 (0.758-1.317) | 0.996 |
| MAP2K2 | 1.267 (1.012-1.586) | 0.039 | 0.942 (0.676-1.313) | 0.726 |
| MMP9 | 1.160 (1.076-1.250) | <0.001 | 0.27 (0.012-6.208) | 0.413 |
| MUC4 | 14.333 (2.951-69.624) | 0.001 | 0.941 (0.534-1.659) | 0.833 |
| NCK1 | 0.550 (0.352-0.859) | 0.009 | 0.998 (0.798-1.248) | 0.984 |
| NFAT5 | 0.682 (0.475-0.980) | 0.039 | 0.973 (0.729-1.299) | 0.852 |
| NR1D1 | 1.168 (1.002-1.360) | 0.047 | 1.046 (0.808-1.353) | 0.734 |
| NR1H2 | 1.433 (1.121-1.832) | 0.004 | 0.936 (0.718-1.22) | 0.624 |
| NR2F1 | 1.155 (1.021-1.308) | 0.023 | 0.783 (0.441-1.39) | 0.404 |
| OGFR | 1.330 (1.045-1.692) | 0.021 | 0.827 (0.606-1.127) | 0.228 |
| PAK6 | 1.475 (1.195-1.821) | <0.001 | 1.166 (0.931-1.462) | 0.181 |
| PDGFRB | 1.402 (1.127-1.743) | 0.002 | 1.094 (0.807-1.482) | 0.564 |
| PGF | 1.273 (1.147-1.412) | <0.001 | 1.169 (0.865-1.58) | 0.31 |
| PIK3CA | 1.137 (1.063-1.215) | <0.001 | 1.38 (0.616-3.094) | 0.434 |
| PLAU | 1.252 (1.064-1.473) | 0.007 | 1.266 (0.939-1.708) | 0.122 |
| PLTP | 1.199 (1.072-1.340) | 0.001 | 1.234 (0.94-1.619) | 0.13 |
| PLXND1 | 1.726 (1.377-2.164) | <0.001 | 1.138 (0.907-1.429) | 0.263 |
| PPARA | 0.541 (0.349-0.840) | 0.006 | 1.047 (0.848-1.292) | 0.668 |
| PSMC6 | 1.238 (1.033-1.485) | 0.021 | 0.782 (0.528-1.159) | 0.221 |
| PTGDS | 1.152 (1.071-1.239) | <0.001 | 0.228 (0.04-1.312) | 0.098 |
| PTGER1 | 1.283 (1.089-1.510) | 0.003 | 0.907 (0.562-1.464) | 0.689 |
| QRFP | 1.330 (1.106-1.599) | 0.002 | 1.019 (0.754-1.378) | 0.904 |
| RABEP2 | 1.284 (1.007-1.638) | 0.044 | 0.954 (0.675-1.349) | 0.791 |
| RAET1E | 1.427 (1.104-1.843) | 0.007 | 1.119 (0.74-1.693) | 0.595 |
| RFX5 | 0.667 (0.459-0.971) | 0.035 | 0.998 (0.779-1.28) | 0.989 |
| RNASE7 | 1.177 (1.045-1.325) | 0.007 | 0.557 (0.24-1.292) | 0.173 |
| RXFP1 | 1.222 (1.005-1.486) | 0.044 | 0.94 (0.621-1.423) | 0.771 |

| | | | | |
|---|---|---|---|---|
| S100A3 | 1.297 (1.170-1.437) | <0.001 | 0.881 (0.596-1.303) | 0.526 |
| SEMA7A | 1.514 (1.298-1.767) | <0.001 | 0.886 (0.598-1.314) | 0.547 |
| SOD1 | 1.284 (1.044-1.579) | 0.018 | 1.08 (0.875-1.333) | 0.473 |
| STAT3 | 0.681 (0.475-0.976) | 0.036 | 0.94 (0.722-1.226) | 0.649 |
| TGFB1 | 1.195 (1.018-1.402) | 0.03 | 0.736 (0.502-1.079) | 0.117 |
| TGFB2 | 0.459 (0.256-0.823) | 0.009 | 1.053 (0.791-1.403) | 0.722 |
| THPO | 1.340 (1.037-1.731) | 0.025 | 0.968 (0.804-1.164) | 0.729 |
| TIE1 | 1.224 (1.020-1.470) | 0.03 | 0.896 (0.646-1.241) | 0.508 |
| TINAGL1 | 1.382 (1.080-1.768) | 0.01 | 1.084 (0.86-1.366) | 0.497 |
| TMSB10 | 1.325 (1.075-1.633) | 0.008 | 0.96 (0.707-1.304) | 0.794 |
| TNFRSF4 | 1.392 (1.154-1.678) | 0.001 | 0.866 (0.62-1.209) | 0.397 |
| TNFRSF6B | 1.268 (1.107-1.452) | 0.001 | 0.734 (0.475-1.134) | 0.164 |
| TOR2A | 1.347 (1.045-1.735) | 0.021 | 0.932 (0.706-1.23) | 0.618 |
| TRPC4AP | 1.185 (1.026-1.368) | 0.021 | 0.978 (0.626-1.526) | 0.921 |
| UNC93B1 | 1.236 (1.052-1.452) | 0.01 | 1.081 (0.833-1.404) | 0.556 |
| VIP | 1.215 (1.054-1.400) | 0.007 | 0.73 (0.472-1.129) | 0.157 |
| HRGs | | | | |
| BGN | 1.205 (1.012-1.434) | 0.036 | 1.005 (0.696-1.451) | 0.978 |
| CDKN1A | 1.283 (1.012-1.625) | 0.039 | 0.822 (0.567-1.191) | 0.301 |
| CP | 1.253 (1.074-1.462) | 0.004 | 1.096 (0.832-1.443) | 0.516 |
| GBE1 | 0.648 (0.428-0.981) | 0.04 | 1.06 (0.863-1.301) | 0.579 |
| GPC1 | 1.195 (1.061-1.345) | 0.003 | 1.008 (0.581-1.749) | 0.978 |
| KDM3A | 0.624 (0.404-0.964) | 0.033 | 1.188 (0.982-1.436) | 0.076 |
| MT2A | 1.247 (1.035-1.503) | 0.02 | 0.775 (0.504-1.192) | 0.246 |
| NAGK | 1.326 (1.030-1.706) | 0.028 | 1.2 (0.98-1.47) | 0.078 |
| PRDX5 | 1.288 (1.042-1.591) | 0.019 | 1.046 (0.801-1.367) | 0.741 |
| S100A4 | 1.162 (1.043-1.294) | 0.007 | 1.045 (0.691-1.582) | 0.833 |
| SERPINE1 | 1.311 (1.169-1.471) | <0.001 | 0.817 (0.57-1.172) | 0.273 |
| SLC25A1 | 1.332 (1.014-1.751) | 0.039 | 1.05 (0.824-1.337) | 0.694 |
| SRPX | 1.355 (1.163-1.578) | <0.001 | 0.92 (0.611-1.387) | 0.692 |
| TGFBI | 1.296 (1.143-1.470) | <0.001 | 1.112 (0.768-1.61) | 0.575 |

**Table S6.** Coefficients of spike-and-slab Lasso Cox and Lasso Cox models

| Gene names | Coefficients |
|---|---|
| IRGs | |
| PAK6 | 0.364613574 |
| PLXND1 | 0.435054147 |
| SEMA7A | 0.251088237 |
| HRGs | |
| BGN | 0.020302494 |
| CP | 0.207320903 |
| GBE1 | -0.373751049 |
| GPC1 | 0.031078184 |
| KDM3A | -0.032321533 |
| NAGK | 0.005800813 |
| S100A4 | 0.083597029 |
| SERPINE1 | 0.199830708 |
| SLC25A1 | 0.117815068 |
| SRPX | 0.108774567 |
| TGFBI | 0.000371747 |

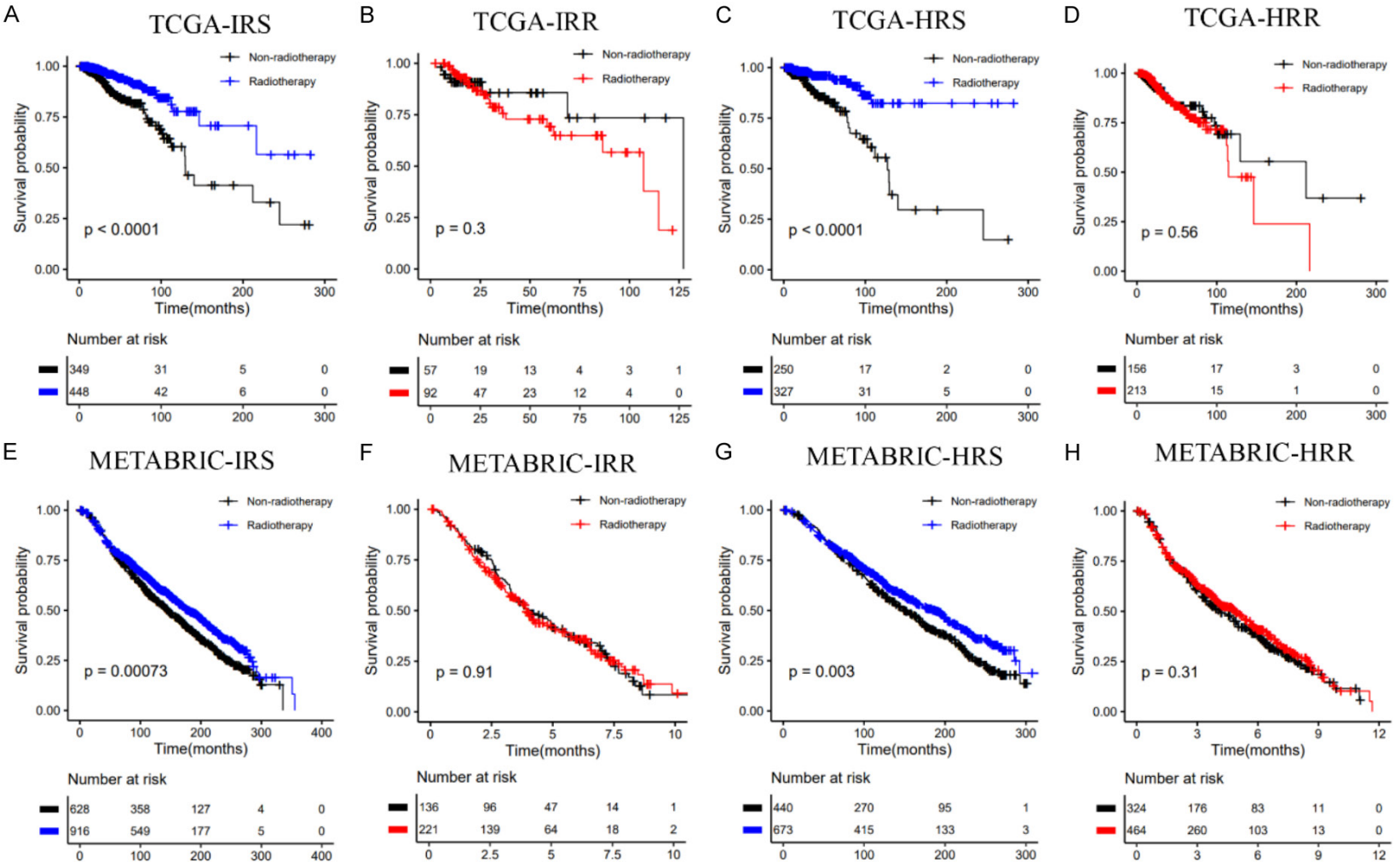


**Figure S4.** Kaplan-Meier curves of OS for patients who had received radiation vs. those who did not: A. TCGA-IRS group; B. TCGA-IRR group; C. TCGA-HRS group; D. TCGA-HRR group; E. METABRIC-IRS group; F. METABRIC-IRR group; G. METABRIC-HRS group; H. METABRIC-HRR group.

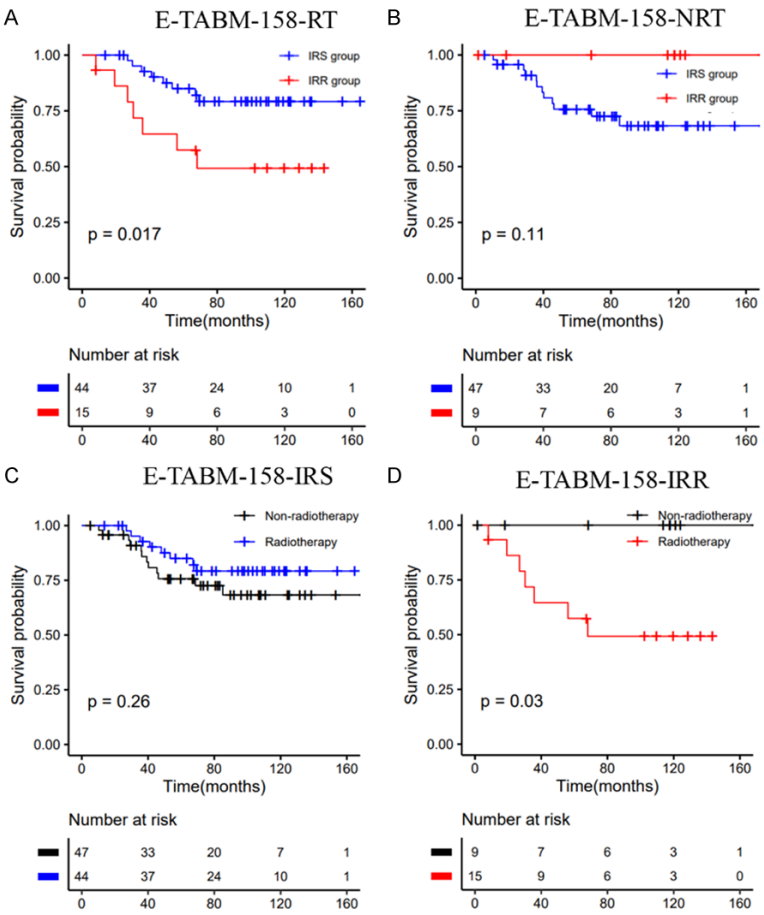


**Figure S5.** Disease-specific survival stratified by the immune signatures in the E-TABM-158 dataset.

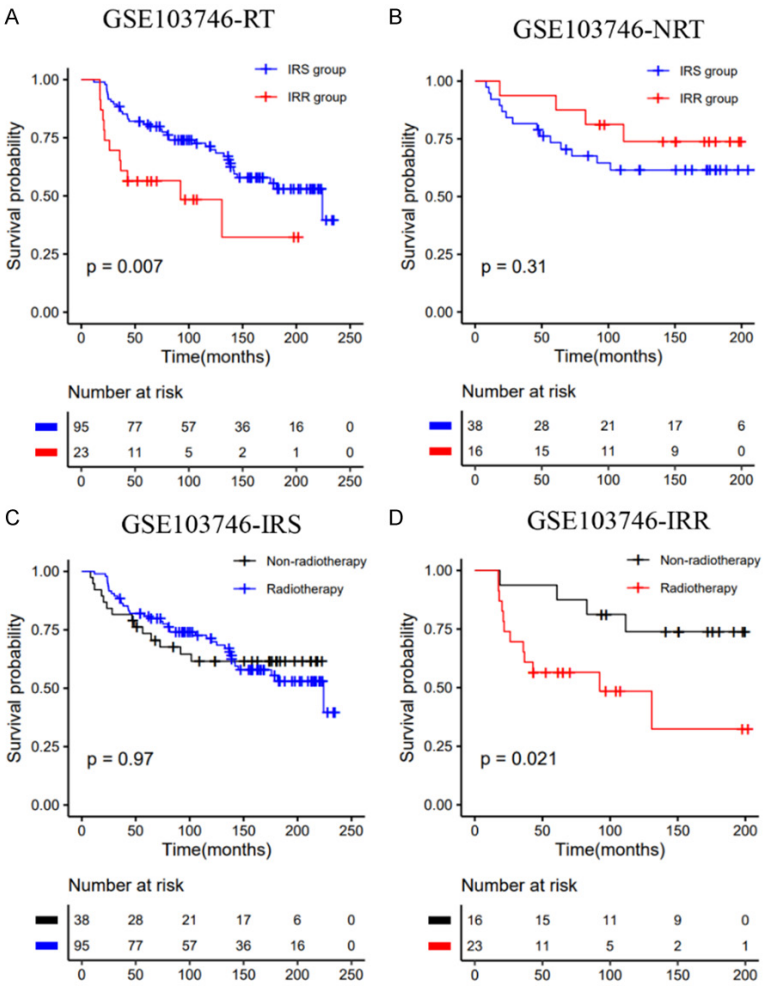


**Figure S6.** Recurrence-free survival stratified by the immune signatures in the GSE103746 dataset.

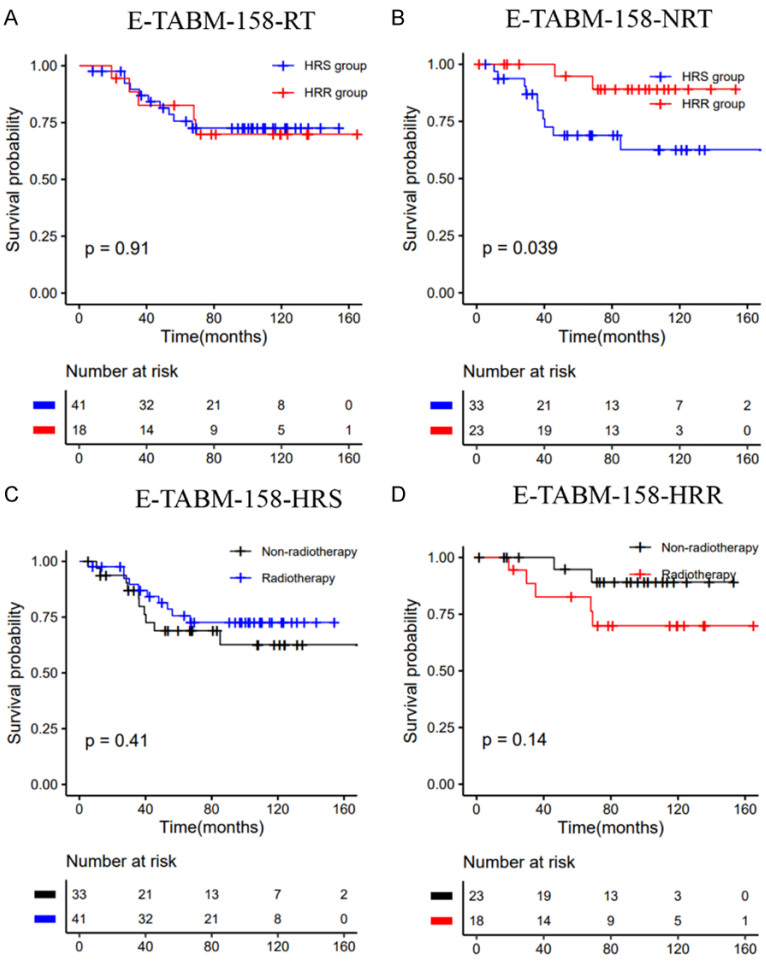


**Figure S7.** Recurrence-free survival stratified by the hypoxia signatures in the E-TABM-158 dataset.

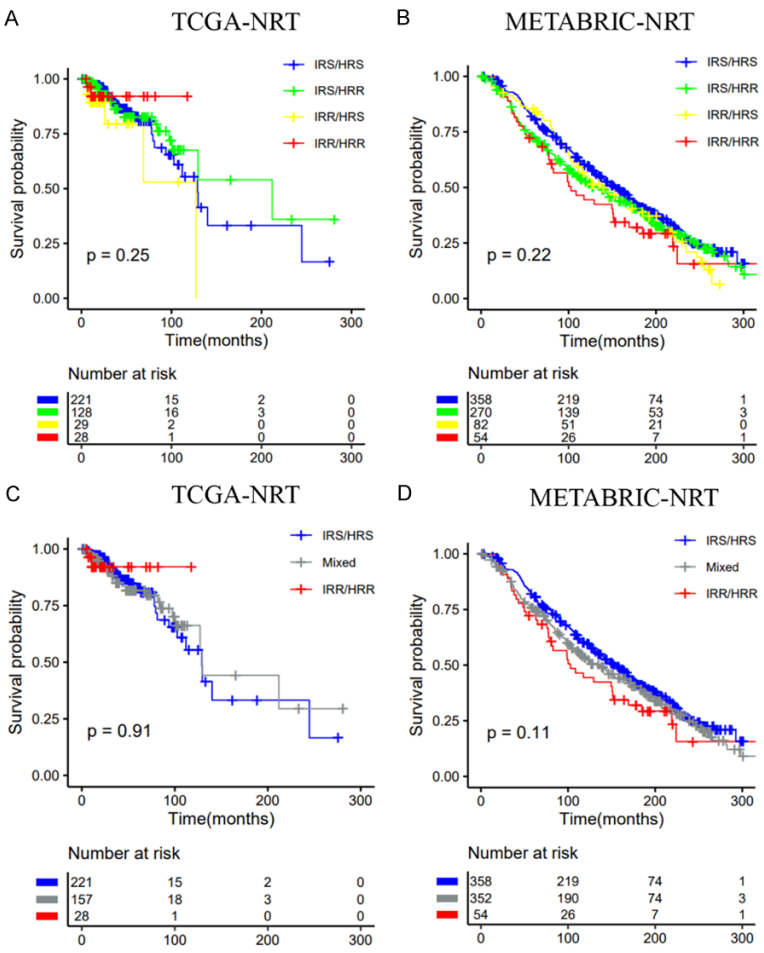


**Figure S8.** Classification of nonradiotherapy patients into subgroups according to the immune signature (IRS vs. IRR) and the hypoxia signature (HRS vs. HRR). A, C. TCGA dataset; B, D. METABRIC dataset.

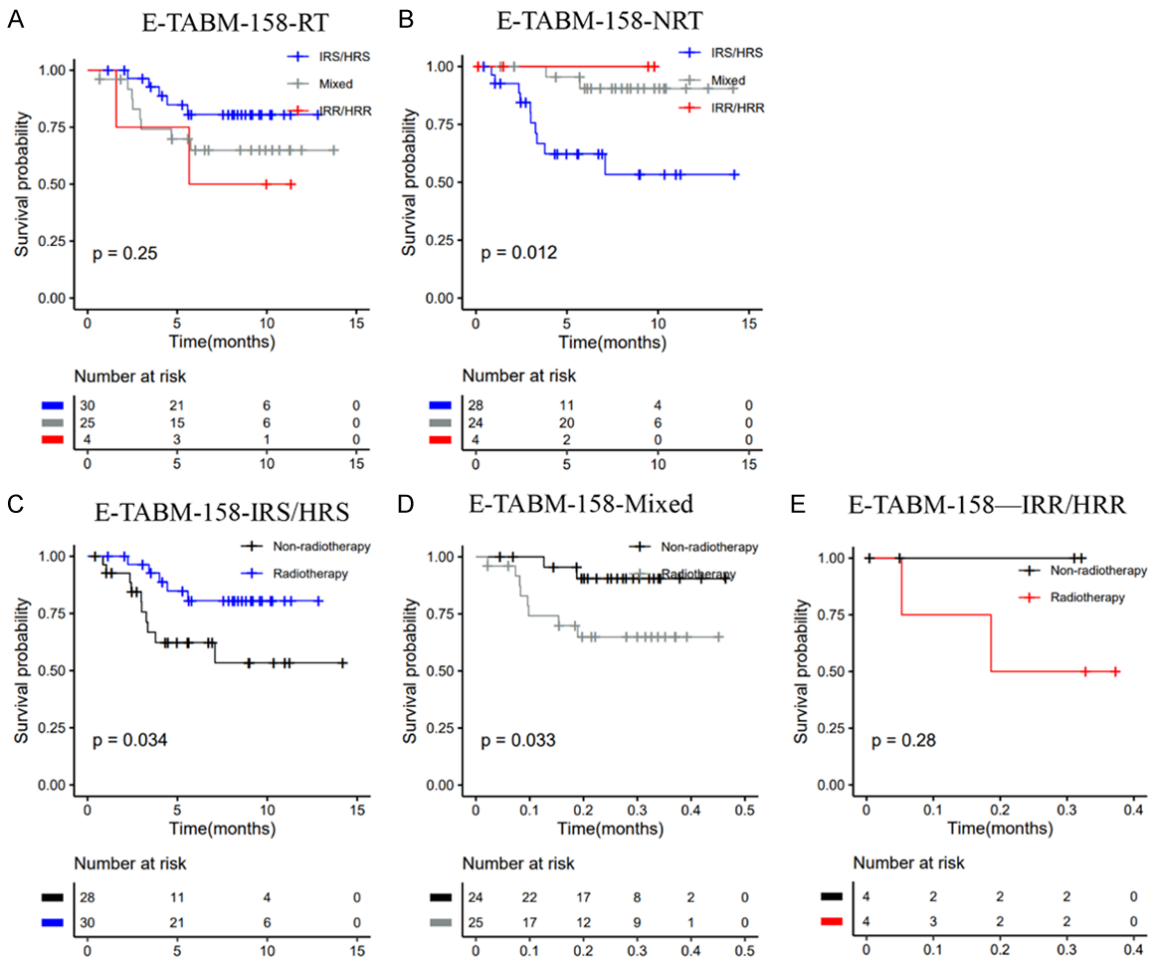


**Figure S9.** Classification of patients into subgroups according to the immune signature (IRS vs. IRR) and the hypoxia signature (HRS vs. HRR) in the E-TABM-158 dataset.

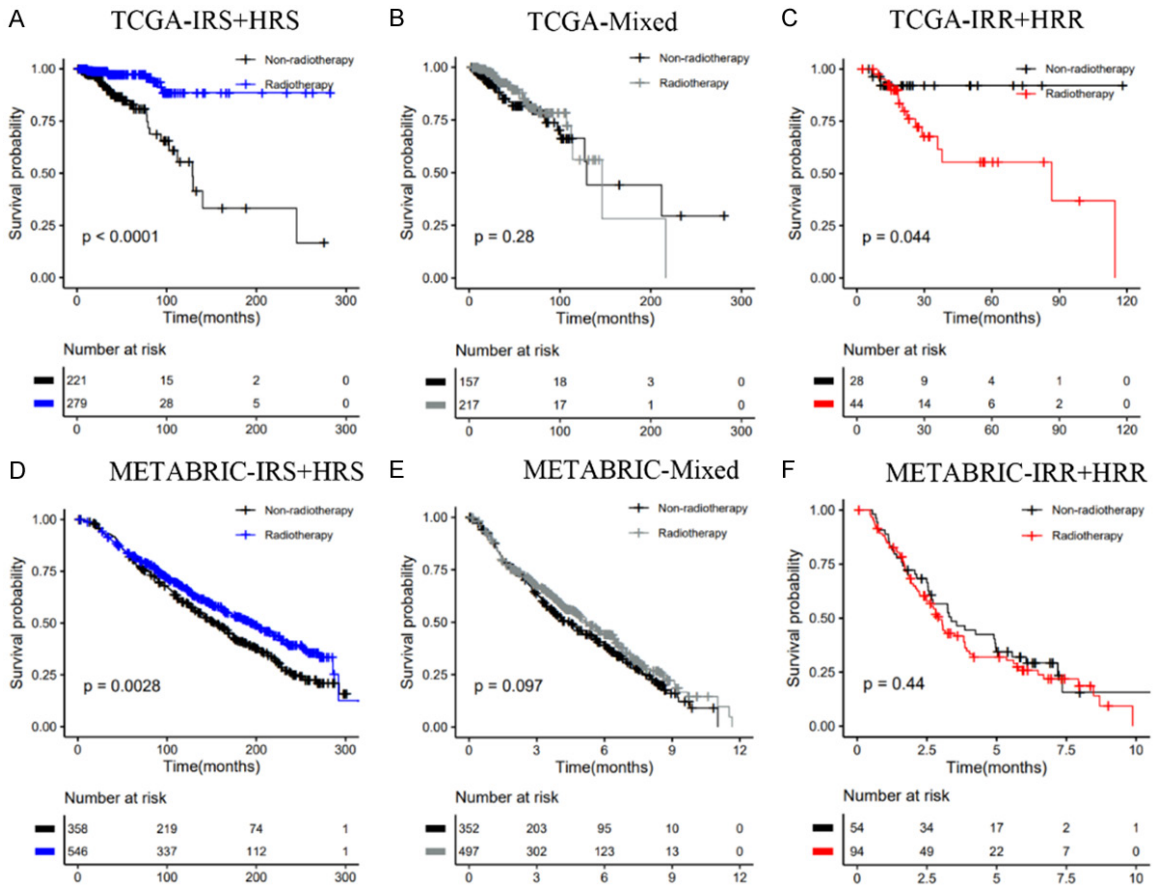


**Figure S10.** Overall survival stratified by the combination of immune and hypoxia gene signatures. A-C. TCGA dataset; D-F. METABRIC dataset.

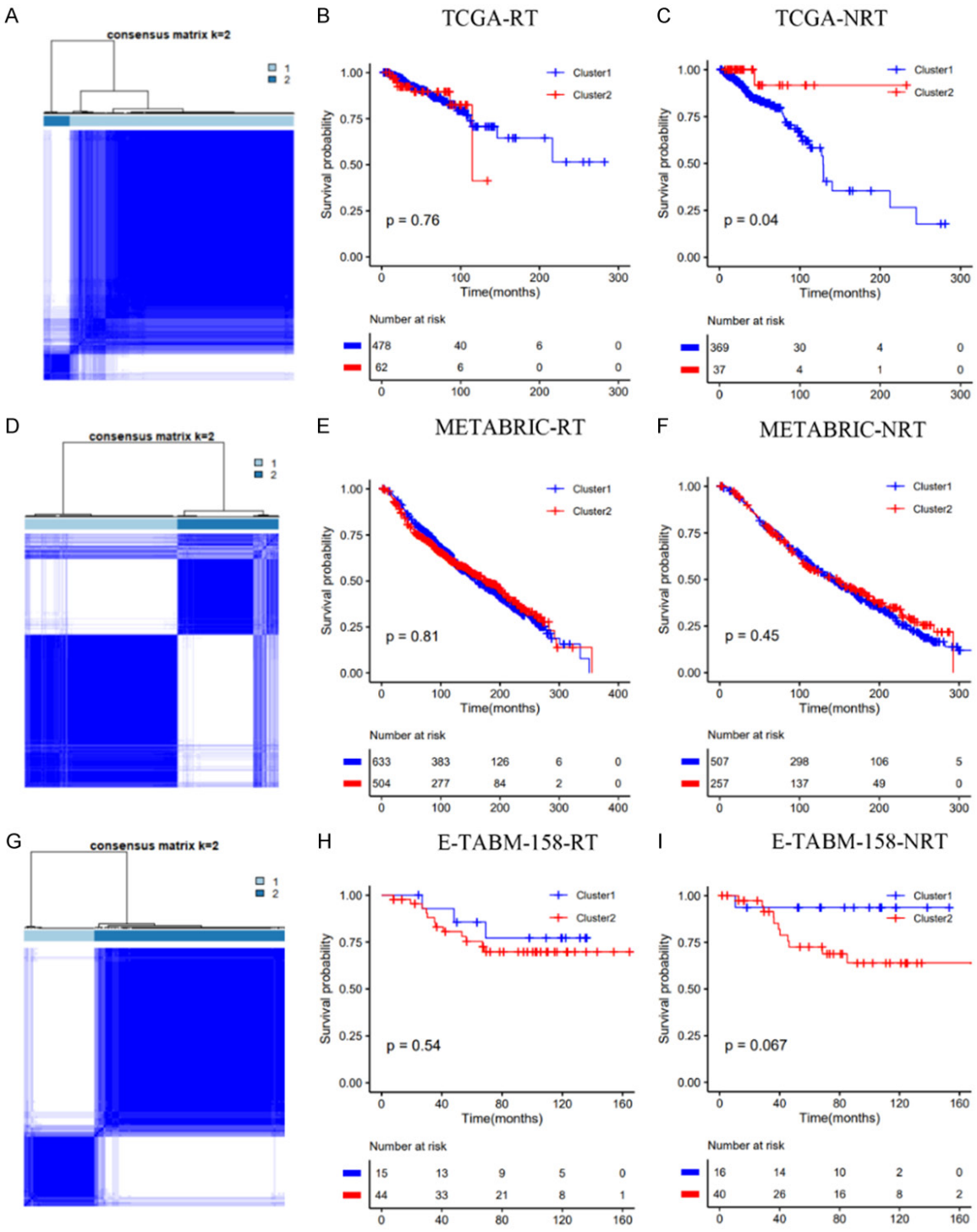


**Figure S11.** Validation of 31-gene in the TCGA, METABRIC, E-TABM-158 datasets. A, D, G. Consensus clustering algorithm generated two clusters based on the expression profile of the 31-gene signature; B, C. Kaplan-Meier plot of OS for the two clusters in the TCGA dataset; E, F. Kaplan-Meier plot of OS for the two clusters in the METABRIC dataset; H, I. Kaplan-Meier plot of DSS for the two clusters in the E-TABM-158 dataset.

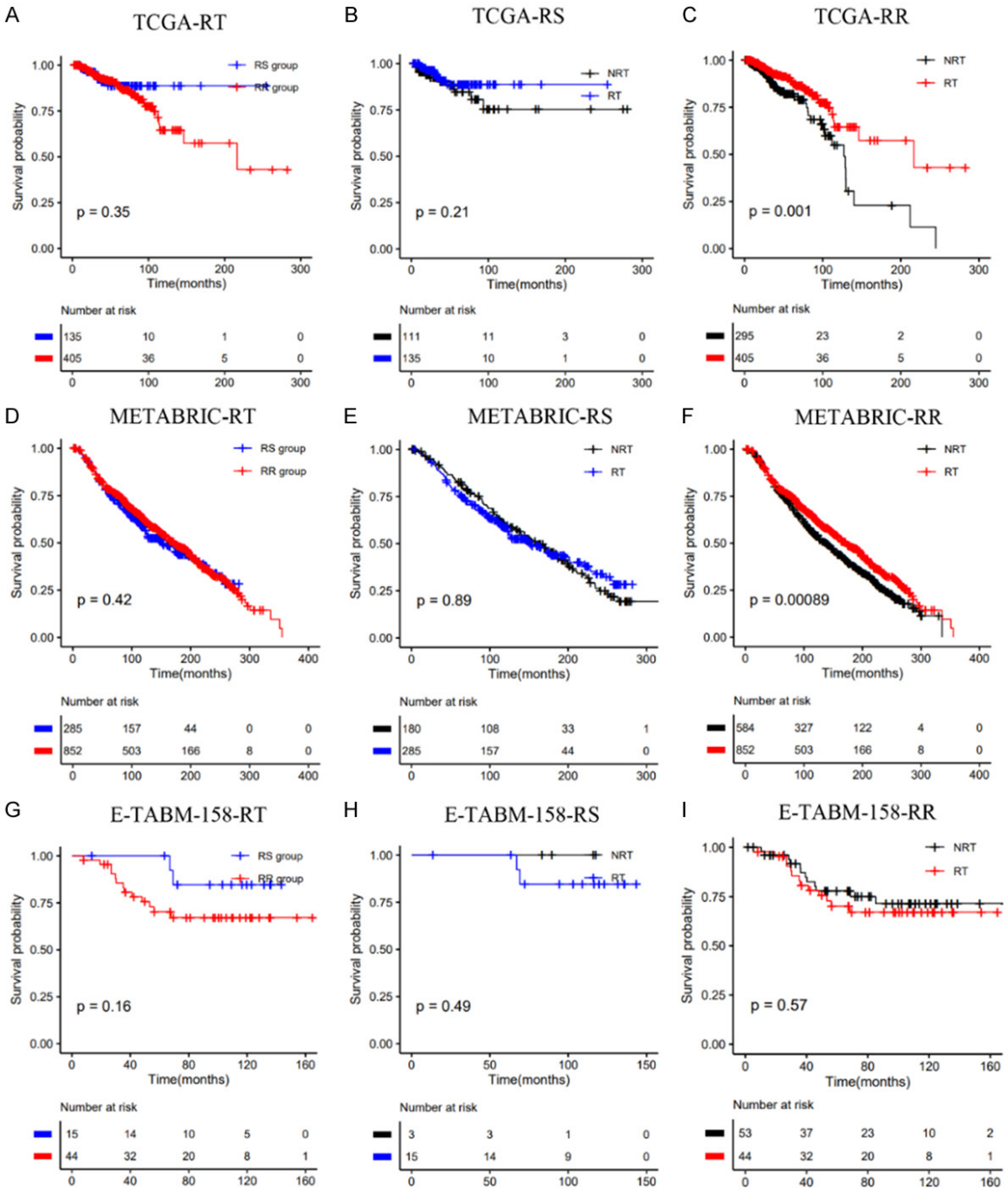


**Figure S12.** Validation of RSI in the TCGA, METABRIC, E-TABM-158 datasets.

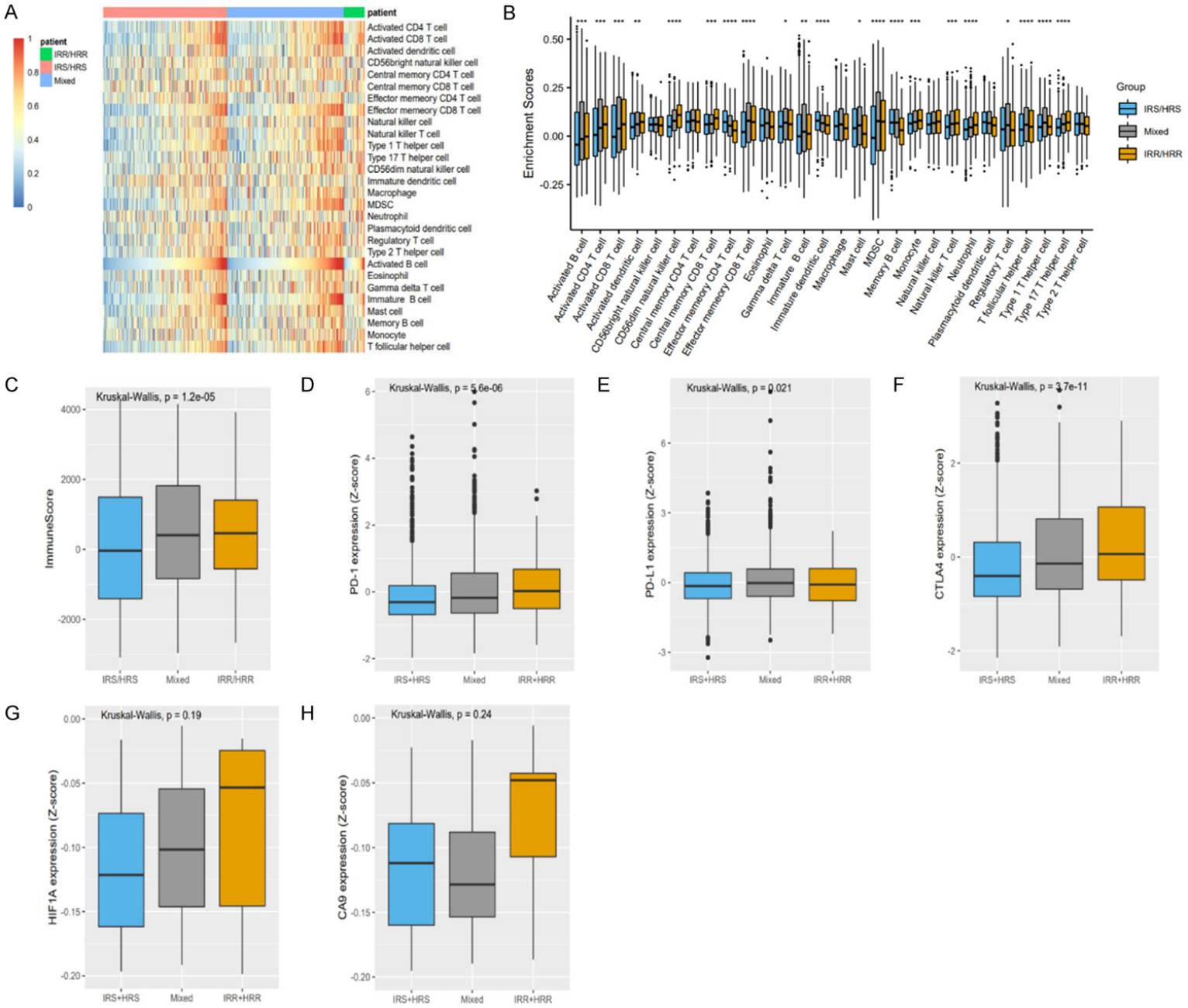
A
patient
IRR/HRR
IRS/HRS
Mixed
Activated CD4 T cell
Activated CD8 T cell
Activated dendritic cell
CD56bright natural killer cell
Central memory CD4 T cell
Central memory CD8 T cell
Effector memeory CD4 T cell
Effector memeory CD8 T cell
Natural killer cell
Natural killer T cell
Type 1 T helper cell
Type 17 T helper cell
CD56dim natural killer cell
Immature dendritic cell
Macrophage
MDSC
Neutrophil
Plasmacytoid dendritic cell
Regulatory T cell
Type 2 T helper cell
Activated B cell
Eosinophil
Gamma delta T cell
Immature B cell
Mast cell
Memory B cell
Monocyte
T follicular helper cell
B
Enrichment Scores
Group
IRS/HRS
Mixed
IRR/HRR
C
Kruskal-Wallis, p = 1.2e-05
ImmuneScore
D
Kruskal-Wallis, p = 5.6e-06
PD-1 expression (Z-score)
E
Kruskal-Wallis, p = 0.021
PD-L1 expression (Z-score)
F
Kruskal-Wallis, p = 3.7e-11
CTLA4 expression (Z-score)
G
Kruskal-Wallis, p = 0.19
HIF1A expression (Z-score)
H
Kruskal-Wallis, p = 0.24
CA9 expression (Z-score)
IRS+HRS
Mixed
IRR+HRR

**Figure S13.** Immune microenvironment of these three groups (IRS/HRS, Mixed, IRR/HRR) in the METABRIC dataset. A, B. ssGSEA analysis showed the immune cell proportions of three groups; C-F. Comparison of immune score, PD-1, PDL-1, CTLA-4 levels of three groups in all patients; G, H. Comparison of HIF-a, CA9 expression levels of three groups in radiotherapy patients.

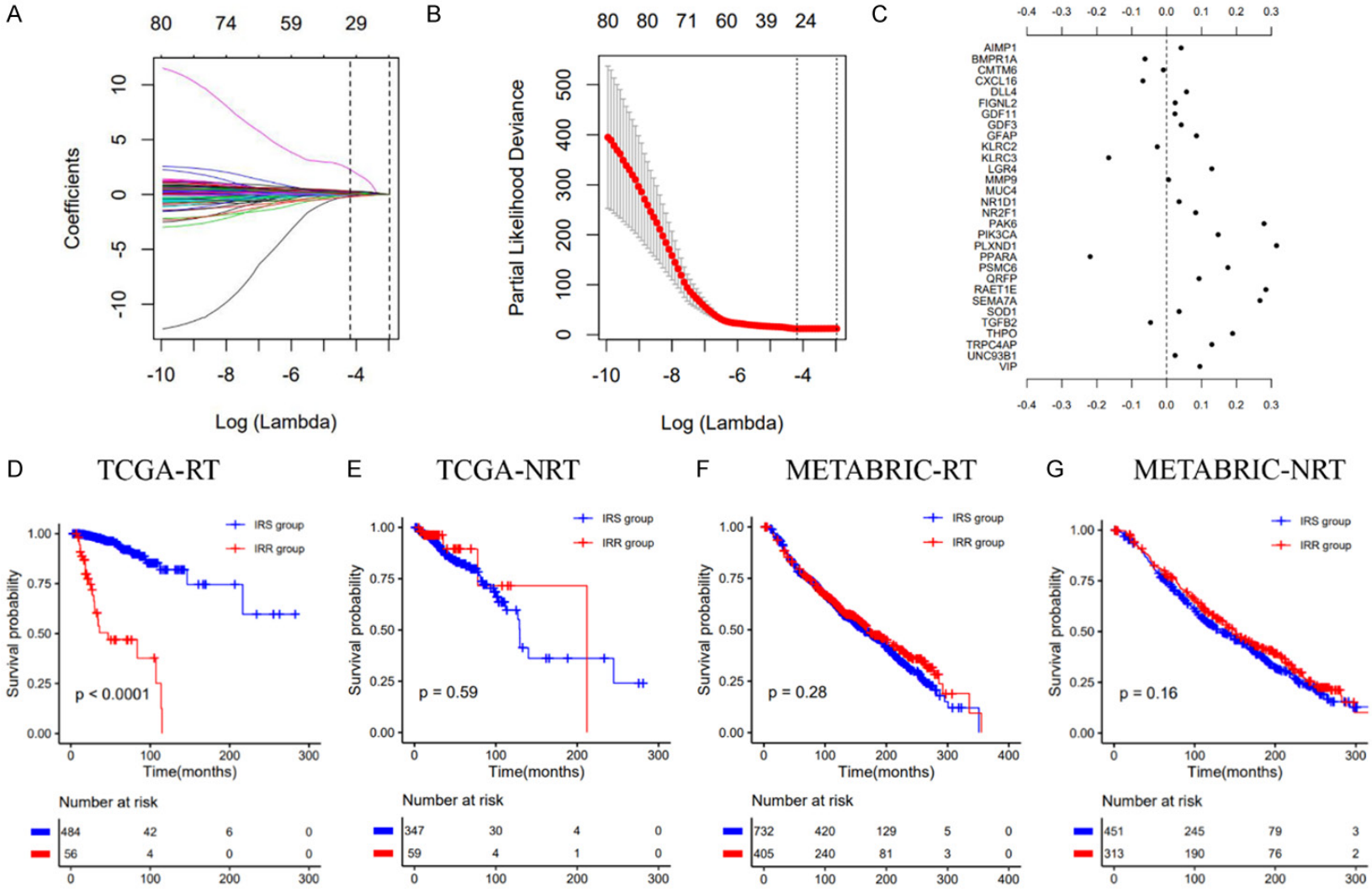


**Figure S14.** A-C. Candidate immune genes selection by Lasso Cox analysis; D-G. Kaplan-Meier survival curves of the IRS group and IRR group in radiotherapy patients and non-radiotherapy patients, respectively.

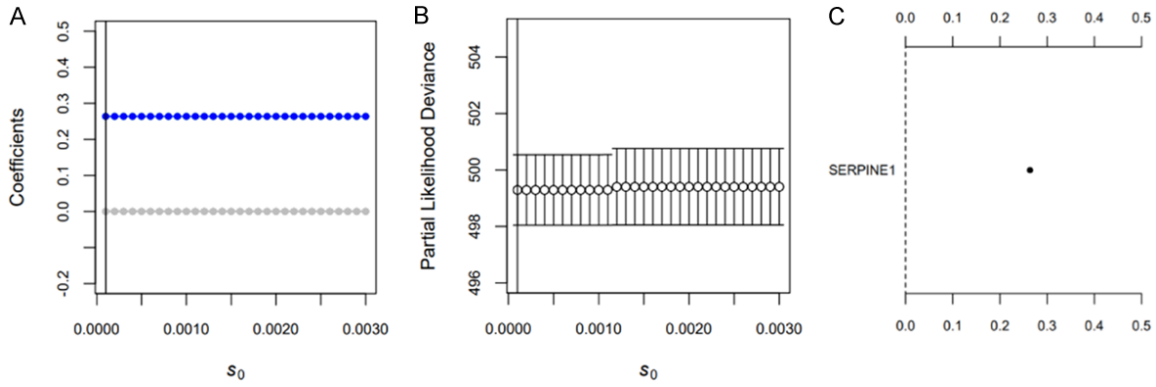


**Figure S15.** A-C. Candidate hypoxia genes selection by spike-and-slab Lasso Cox analysis.