**Supplementary Table 4:** Univariate and Multivariate Overall Survival Cox proportional hazards regression including ICR Cluster, Stage, Mutational Rate, Aneuploidy Score, Proliferation ES, and TGF beta signaling ES, in all cancer types and stratified according to ICR-enabling status. HRs (hazard ratios) for death. Multivariate was stratified by stage/grade. In the “Cancer-type adjusted multivariate stratified by stage/grade”, tumor mutation rate, aneuploidy score, proliferation and TGF-beta scores were normalized by cancer (mean-centered in each cancer type). HPA significant violations were detected only for “stage/grade” in the models that included all cancer types and in the one that included “enabled and disabled” tumor types, in which a multivariate stratified model was run. For symmetry, stratification by “stage/grade” was also performed in the model that includes “disabled” tumor types. ICR cluster entered as categorical (factor) variable (factor levels: “ICR High”, “ICR Low”) Stage is coded as Stage I = 1; Stage II = 2; Stage III = 3; Stage IV = 4. Histologic grade was used for gliomas (LGG and GBM) instead of stage (LGG Grade 2 = 2; LGG Grade 3 = 3, Grade 4 (GBM) = 4). Only samples with all the variables available are included in the univariate and multivariate analyses. HRs (hazard ratios) for death. Signif. codes: *** <0.001; ** <0.01; * <0.05. # Significant violation of proportional hazards assumption (PHA). ES: enrichment score.

|  | **Univariate** |  | **Multivariate** |  | **Multivariate stratified by stage/grade** |  | **Cancer-type adjusted multivariate stratified by stage/grade** |  |
|---|---|---|---|---|---|---|---|---|
| **Variables** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** |
| **Samples from all cancer types (n = 4307)** |  |  |  |  |  |  |  |  |
| ~ ICR cluster (ICR Low vs. High) | 1.25 (1.115- 1.401) | 0.000133 *** | 1.370 (1.2044- 1.559) | 1.73e-06 *** | 1.355 (1.1904- 1.543) | 4.31e-06 *** | 1.3595 (1.1929-1.549) | 4.12e-06 *** |
| ~ Pathologic Stage/Grade | 1.838 (1.724- 1.96) | <2e-16*** | 1.727 (1.6184- 1.842) # | < 2e-16*** | strata |  | strata |  |
| ~ Tumor mutational rate | 1.403 (1.296-1.519) | <2e-16*** | 1.177 (1.0584- 1.308) | 0.00261** | 1.185 (1.0639- 1.319) | 0.00202 ** | 0.9686 (0.9051-1.037) | 0.358 |
| ~ Aneuploidy score | 1.027 (1.021- 1.033) | <2e-16 *** | 1.003 (0.9955- 1.011) | 0.41578 | 1.003 (0.9952- 1.011) | 0.45398 | 1.0301 (0.9690-1.095) | 0.342 |
| ~ Proliferation ES | 5.256 (4.077- 6.774) | <2e-16 *** | 3.485 (2.447- 4.963) | 4.44e-12 *** | 3.417 (2.3926- 4.880) | 1.41e-11 *** | 13.7999 (6.4728-29.421) | 1.08e-11 *** |
| ~ TGF beta signaling ES | 3.119 (2.104- 4.623) | 1.5e-08*** | 4.770 (3.092- 7.359) | 1.64e-12 *** | 4.985 (3.2260- 7.702) | 4.64e-13 *** | 5.5143 (2.9090-10.453) | 1.67e-07 *** |
| **Samples from ICR-enabled cancer types (n = 1648)** |  |  |  |  |  |  |  |  |
| ~ ICR cluster (ICR Low vs. High) | 1.677 (1.405- 2.001) | 1.02e-08 *** | 1.624 (1.3268- 1.988) | 2.57e-06 *** | 1.625 (1.3278- 1.990) | 2.51e-06 *** | 1.5587 (1.2750-1.9054) | 1.49e-05 *** |
| ~ Pathological Stage | 1.833 (1.654- 2.032) | <2e-16 *** | 1.719 (1.5463- 1.911) # | < 2e-16*** | strata |  | strata |  |
| ~ Tumor mutational rate | 1.026 (0.9243- 1.138) | 0.632 | 1.050 (0.9052- 1.219) | 0.5177 | 1.049 (0.9040- 1.217) | 0.5289 | 0.8658 (0.7875-0.9519) | 0.0029 ** |
| ~ Aneuploidy score | 1.015 (1.004- 1.025) | 0.00636 ** | 1.001 (0.9886- 1.013) | 0.9065 | 1.001 (0.9891- 1.014) | 0.8382 | 1.0265 (0.9340-1.1283) | 0.5870 |
| ~ Proliferation ES | 2.365 (1.448- 3.861) | 0.000583 *** | 2.326 (1.221- 4.432) | 0.0103 * | 2.352 (1.2307- 4.493) | 0.00965 ** | 2.3946 (1.1805-4.8571) | 0.0155 * |
| ~ TGF beta signaling ES | 2.674 (1.692- 4.227) | 2.55e-05 *** | 1.971 (1.150- 3.379) | 0.0135 * | 1.912 (1.1172- 3.273) | 0.01807 * | 1.5918 (0.7554-3.3542) | 0.2215 |
| **Samples from ICR-disabled cancer types (n = 617)** |  |  |  |  |  |  |  |  |
| ~ ICR cluster (ICR Low vs. High) | 0.6147 (0.4623- 0.8175) | 0.000821 *** | 1.063 (0.7759- 1.456) | 0.70407 | 0.943 (0.680- 1.308) | 0.724 | 1.017 (0.7254-1.425) | 0.924 |
| ~ Pathological Stage/Grade | 1.461 (1.232- 1.734) | 1.37e-05 *** | 1.337 (1.1137- 1.606) | 0.00185** | strata |  | strata |  |
| ~ Tumor mutational rate | 1.285 (0.9792- 1.686) | 0.0705 | 0.921 (0.753- 1.126) | 0.42015 | 0.9618 (0.7763-1.192) | 0.722 | 1.116 (0.9584-1.299) | 0.158 |
| ~ Aneuploidy score | 1.032 (1.015- 1.049) | 0.000177 *** | 1.001 (0.9832- 1.020) | 0.88122 | 0.9992 (0.9803-1.018) | 0.933 | 1.076 (0.9552-1.213) | 0.227 |
| ~ Proliferation ES | 48.25 (22.8- 102.1) | <2e-16*** | 27.891 (11.795- 65.955) | 3.47e-14 *** | 27.16 (11.37-64.91) | 1.08e-13 *** | 47.571 (13.4213-168.613) | 2.20e-09 *** |
| ~ TGF beta signaling ES | 21.05 (9.339-47.47) | 2.04e-13 *** | 13.192 (5.911- 29.442) | 3.01e-10 *** | 12.2607 (5.44-27.63) | 1.49e-09 *** | 23.197 (5.1635-104.216) | 4.11e-05 *** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Samples from ICR neutral cancer types (n = 2042)** | | | | | | | | | |
| ~ | ICR cluster (ICR Low vs. High) | 1.181 (0.9873- 1.412) | 0.0688 | 1.300 (1.0484- 1.613) | 0.016833 * | 1.300 (1.0469-1.615) | 0.017555 * | 1.296 (1.0449-1.607) | 0.01825 * |
| ~ | Pathological Stage/Grade | 1.959 (1.781- 2.154) | <2e-16 *** | 1.958 (1.7693- 2.167) # | < 2e-16*** | strata | | strata | |
| ~ | Tumor mutational rate | 1.992 (1.751- 2.265) | <2e-16 *** | 1.714 (1.4230- 2.065) | 1.4e-08*** | 1.724 (1.4297- 2.079) | 1.18e-08 *** | 1.044 (0.9298-1.172) | 0.46739 |
| ~ | Aneuploidy score | 1.038 (1.028- 1.048) | 2.76e-15 *** | 1.005 (0.9925- 1.017) | 0.463756 | 1.004 (0.9914- 1.016) | 0.565784 | 0.991 (0.8910-1.102) | 0.86762 |
| ~ | Proliferation ES | 7.371 (5.208- 10.43) | <2e-16 *** | 2.331 (1.411- 3.849) | 0.000949 *** | 2.464 (1.4720- 4.125) | 0.000602 *** | 8.955 (3.0166-26.585) | 7.85e-05 *** |
| ~ | TGF beta signaling ES | 3.015 (1.589- 5.72) | 0.000733 *** | 1.246 (0.604- 2.570) | 0.551416 | 1.337 (0.6406- 2.791) | 0.439147 | 2.694 (1.3394-5.417) | 0.00544 ** |

Signif. codes: *** <0.001; ** <0.01; * <0.05
[#] Significant violation of proportional hazards assumption (PHA)

In the “Cancer-type adjusted multivariate stratified by stage/grade”, tumor mutation rate, aneuploidy score, proliferation and TGF-beta scores were normalized by cancer (mean-centered in each cancer type). PHA significant violations were detected only for “stage/grade” in the models that included all cancer types and in the one that included “enabled and disabled” tumor types, in which a multivariate stratified model was run. For symmetry, stratification by “stage/grade” was also performed in the model that includes “disabled” tumor types.

ICR cluster entered as categorical (factor) variable (factor levels: “ICR High”, “ICR Low”)
Stage is coded as Stage I = 1; Stage II = 2; Stage III = 3; Stage IV = 4. Histologic grade was used for gliomas (LGG and GBM) instead of stage (LGG Grade 2 = 2; LGG Grade 3 = 3, Grade 4 (GBM) = 4). Only samples with all the variables available are included in the univariate and multivariate analyses.
HRs (hazard ratios) for death.