Figure S1

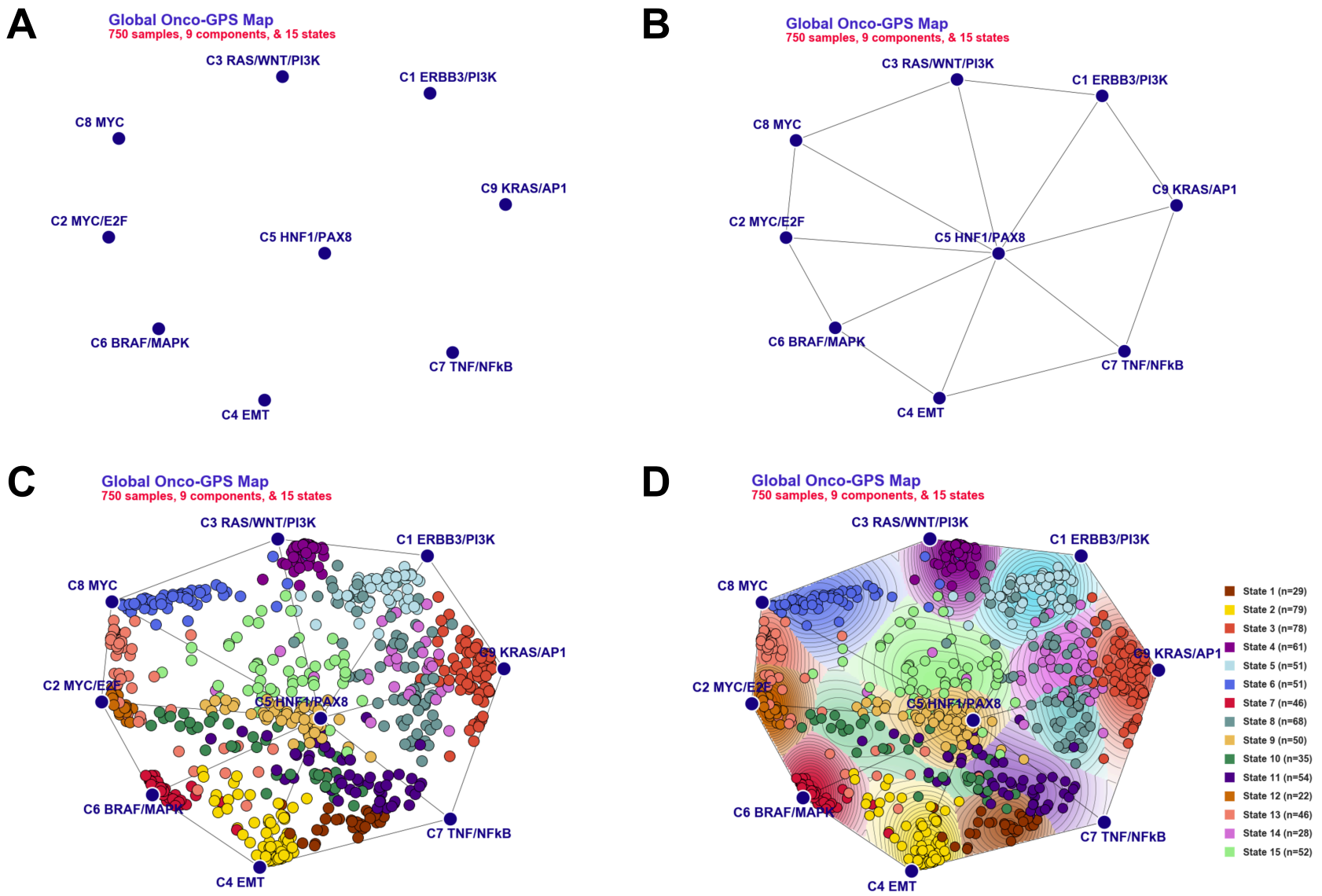

Figure S1. **Related to main Figure 1 and 6.** Generation of general (global) *Onco*-GPS layout: A) compute location of component nodes using a Sammon map projection, B) Add lines connecting component nodes using Delaunay triangulation, C) projection of individual cancer samples, and D) adding contours and color background to represent *Onco*-GPS states.

Figure S2

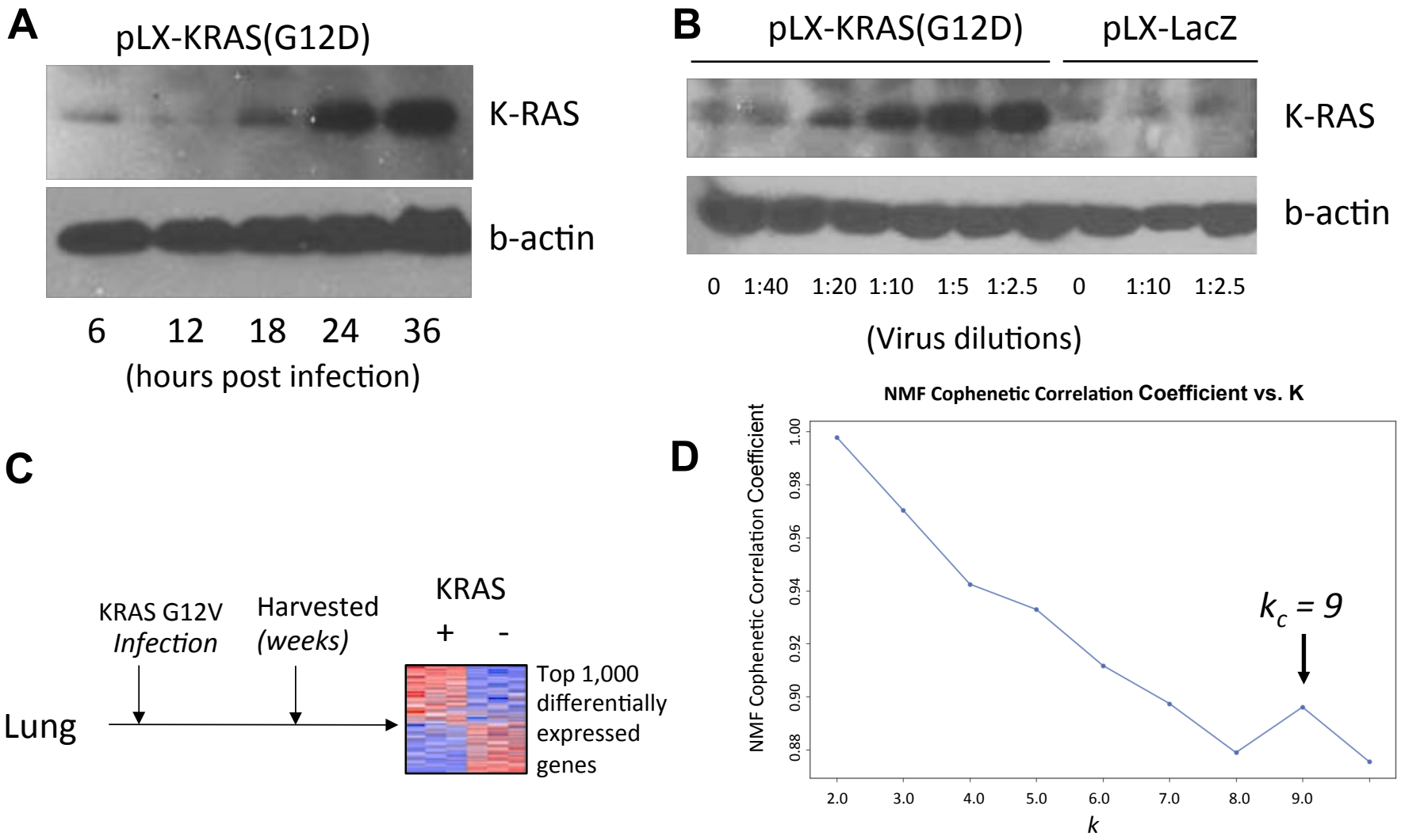

Figure S2. Related to main Figure 2 and 3. Optimization of **A)** dynamics and B) viral titers to induce KRAS activation; C) *KRAS* isogenic system generated from human lung cells. D) Stability of the *Onco*-GPS NMF matrix decomposition. The graph shows the cophenetic coefficient as a function of component number. A peak in the cophenetic coefficient at k = 9 indicates a stable solution with 9 components.

Figure S3

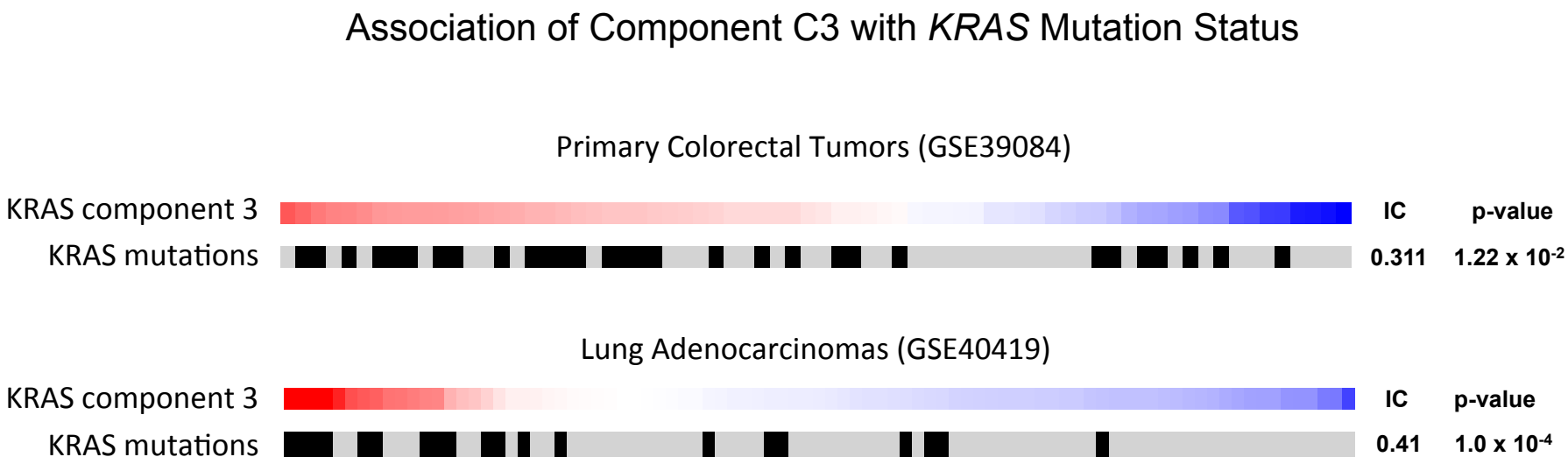

Figure S3. Related to main Figure 4. Association of component *C3* with *KRAS* mutation status in primary colorectal (GEO dataset GSE39084) and lung adenocarcinomas (GEO dataset GSE40419).

Figure S4

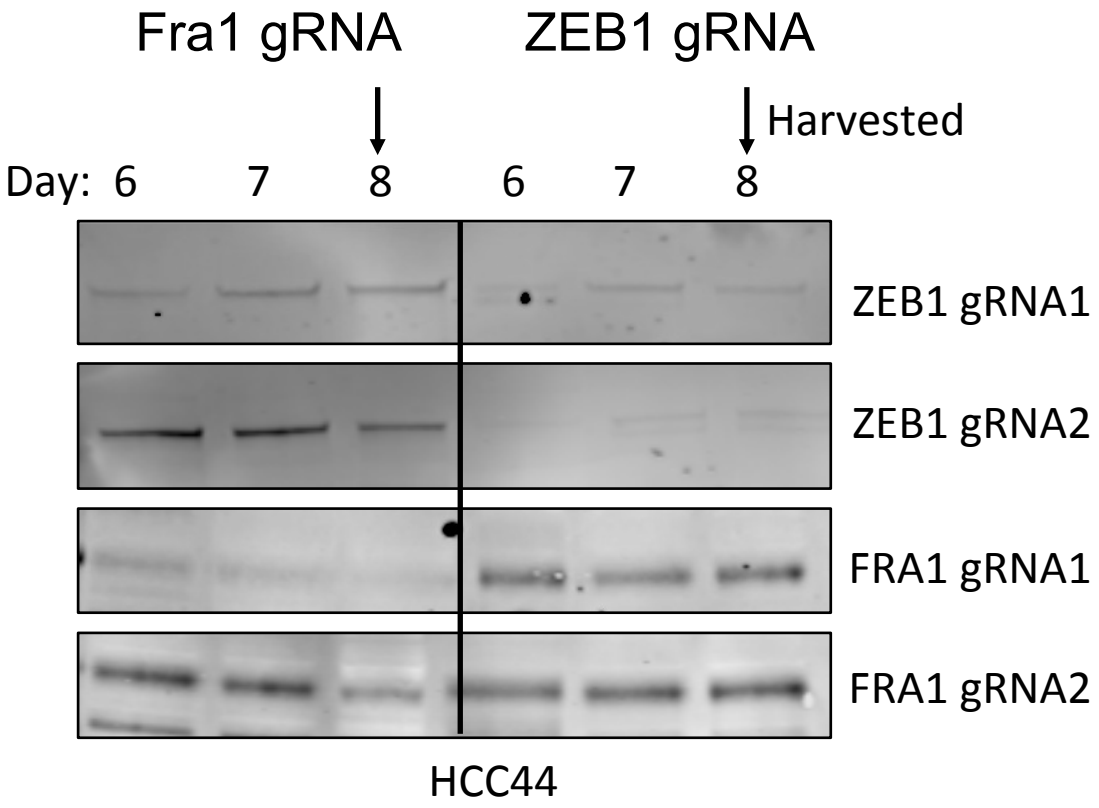

Figure S4. Related to main Figure 5. Confirmation of dynamics of protein decrease upon deletion of *FOSL1/FRA1* and *ZEB1* using gRNA CRISPR-*CAS9* using immunoblotting. By day 8, the majority of proteins were suppressed and this day's sample was used for mRNA profiling.

Figure S5

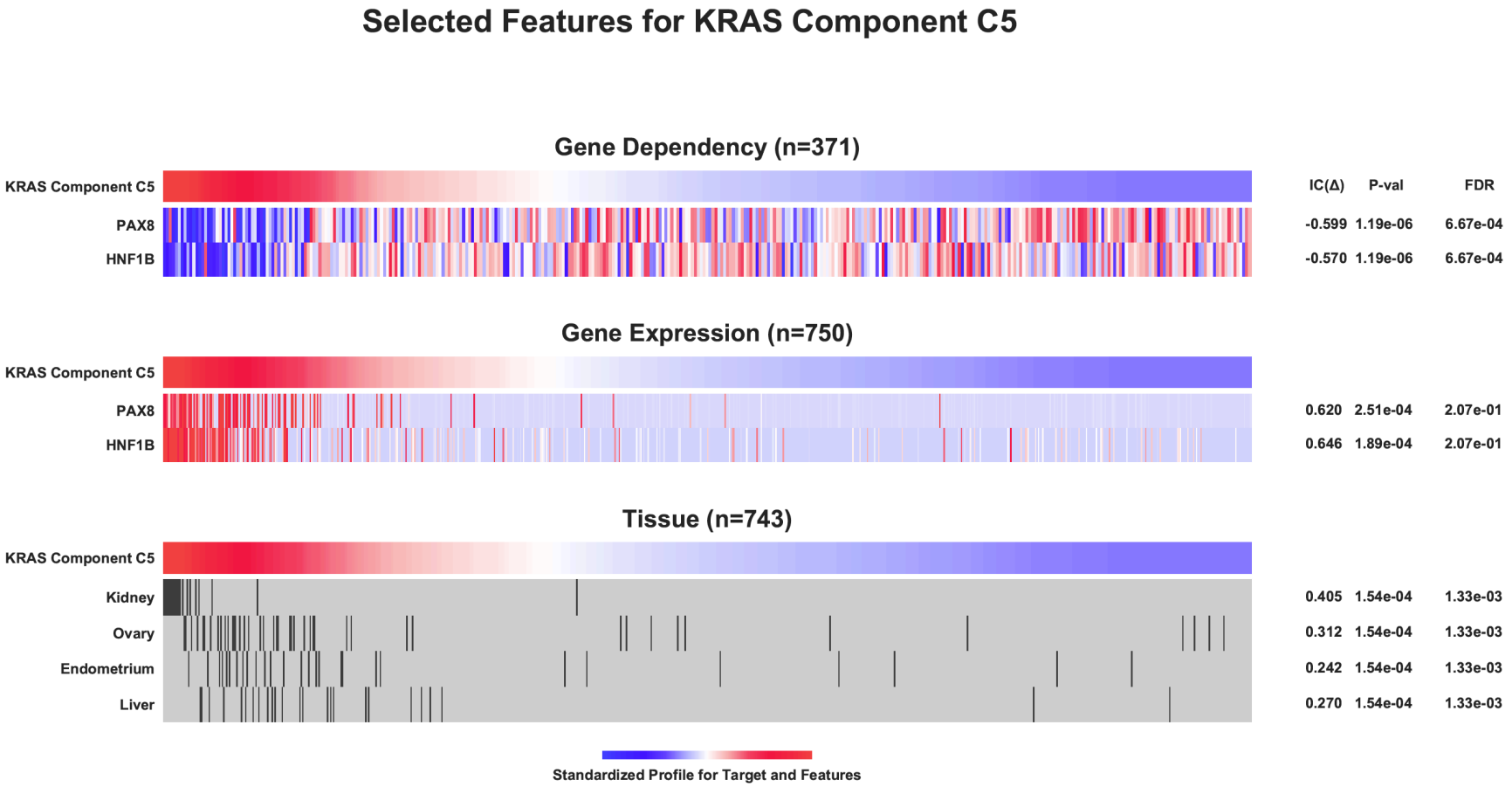

Figure S5. Related to main Figure 5. Selected features associated with component *C5* in CCLE and Achilles datasets. Component *C5* scores were associated with top features in Top) expression levels of PAX8 and HNF1B, Middle) PAX8 and HNF1B dependency from Achilles RNAi data, and Bottom) tissue type.

Figure S6

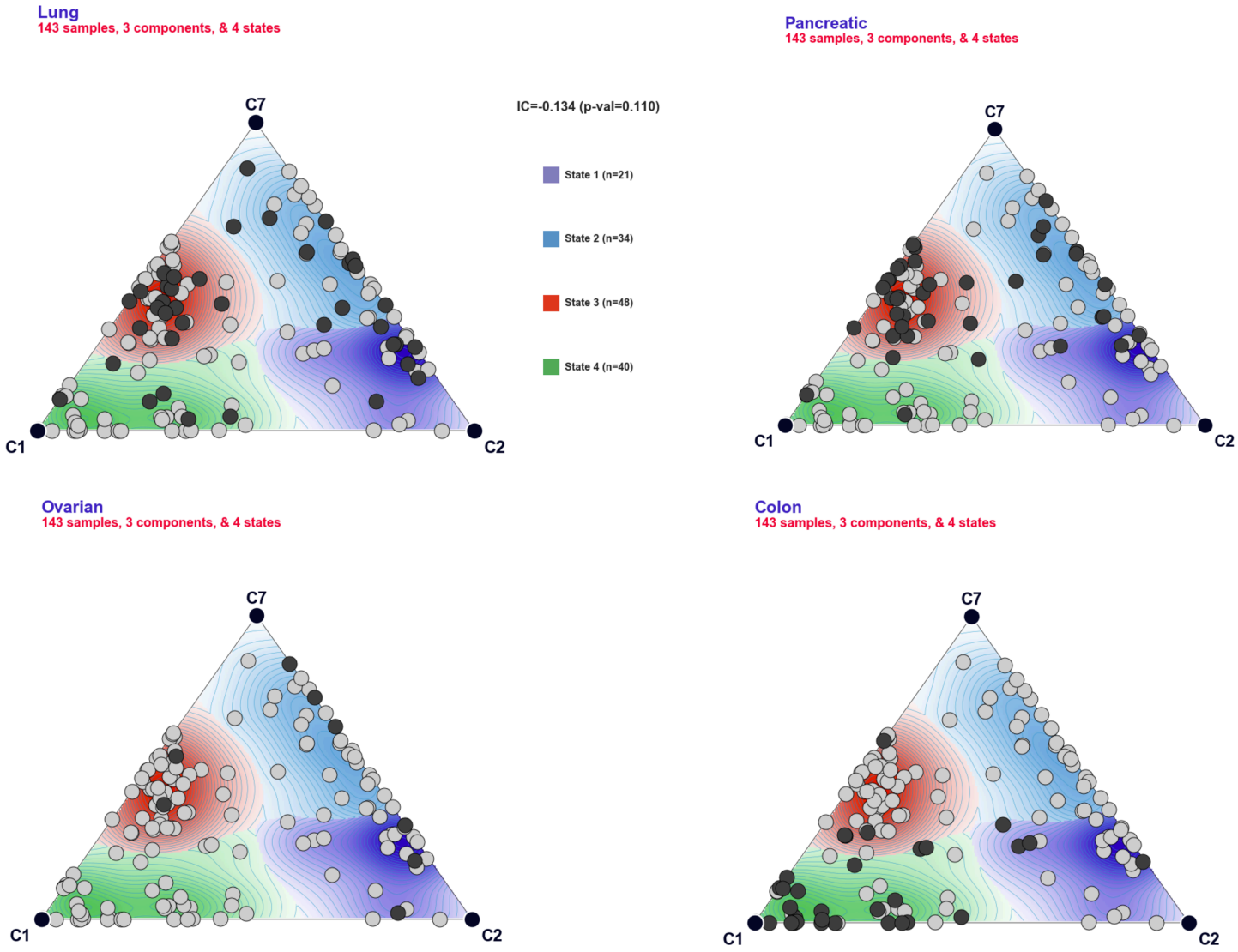

Figure S6. **Related to main Figure 6.** 4 Major tissue representations of KRAS mutant cancers across 4 cell states in the KRAS Onco-GPS map.

Figure S7

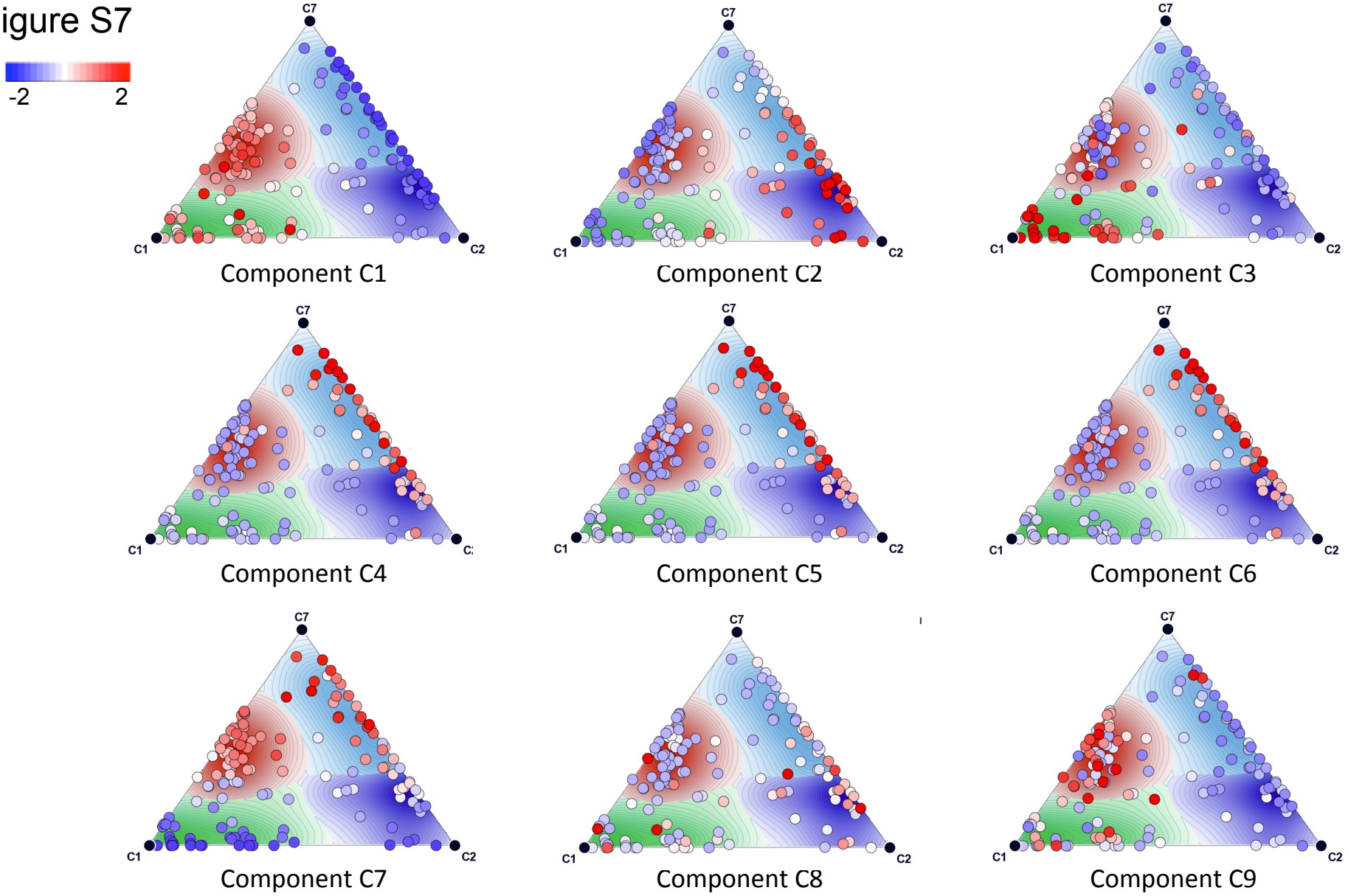

Figure S7. **Related to main Figure 6.** *Onco*-GPS maps defined by components *C1-C7-C2* and the individual component scores projected as features (red-high, blue-low).

Figure S8

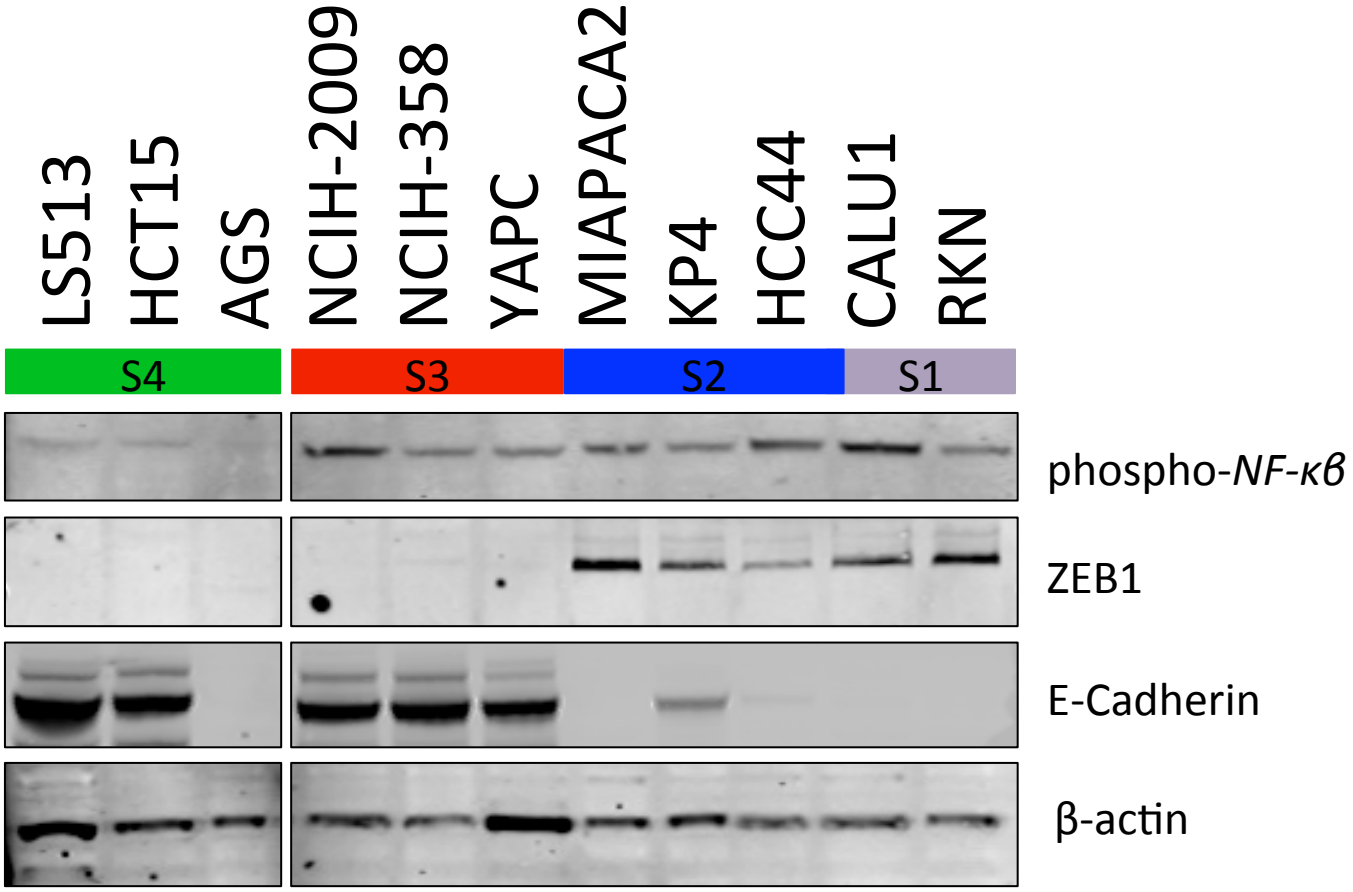

Figure S8. **Related to main Figure 6**. Immunoblots representing assessment of markers of epithelial-EMT state, and activation of NF-κB pathway across *KRAS* mutant cancers defined by KRAS *Onco*-GPS.

Figure S9

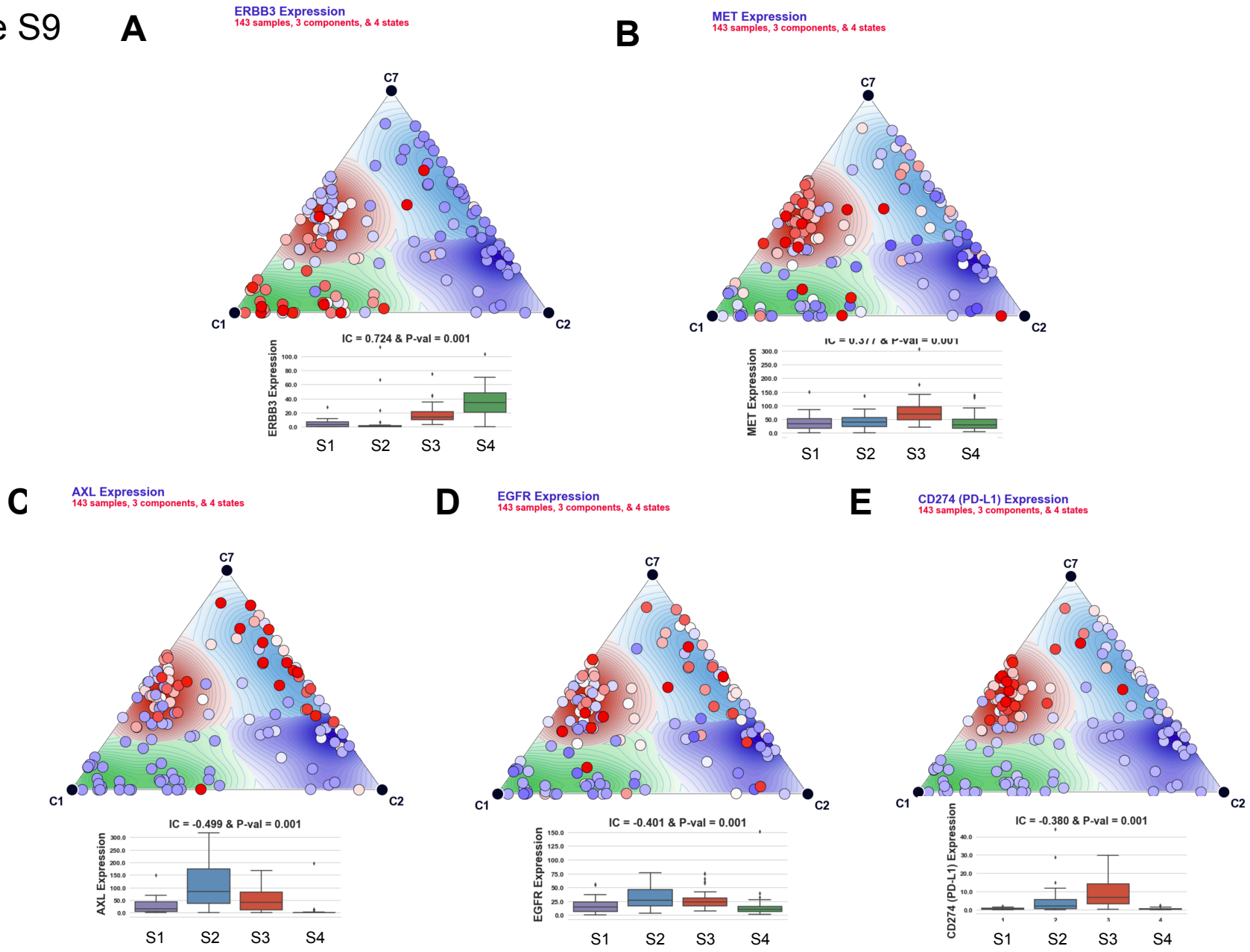

Figure S9. **Related to main Figure.** *Onco*-GPS maps and boxplots depicting transcript levels of RTKs: A) ERBB3, B) MET, C) AXL, D) EGFR and E) CD274 (PDL-1) in the *S1-S4 KRAS* mutant *Onco*-GPS states.

Figure S10

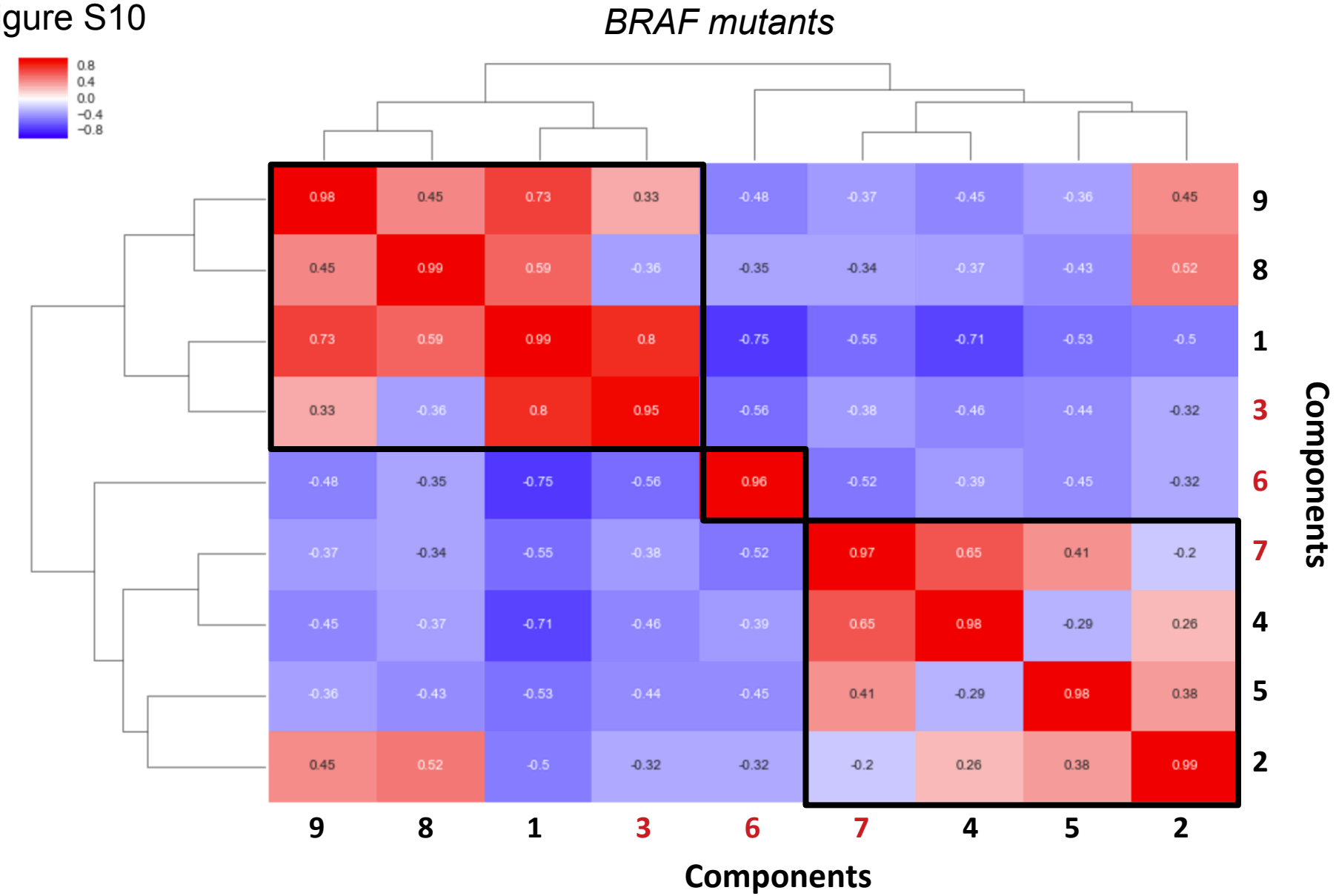

Figure S10. **Related to main Figure 7.** Association matrix of the 9 KRAS components (*C1-C9*) with each other according to the Information Coefficient (IC) in *BRAF* mutant samples. Components highlighted in red depict components that were chosen as representative components for subsequent analysis.

Figure S11

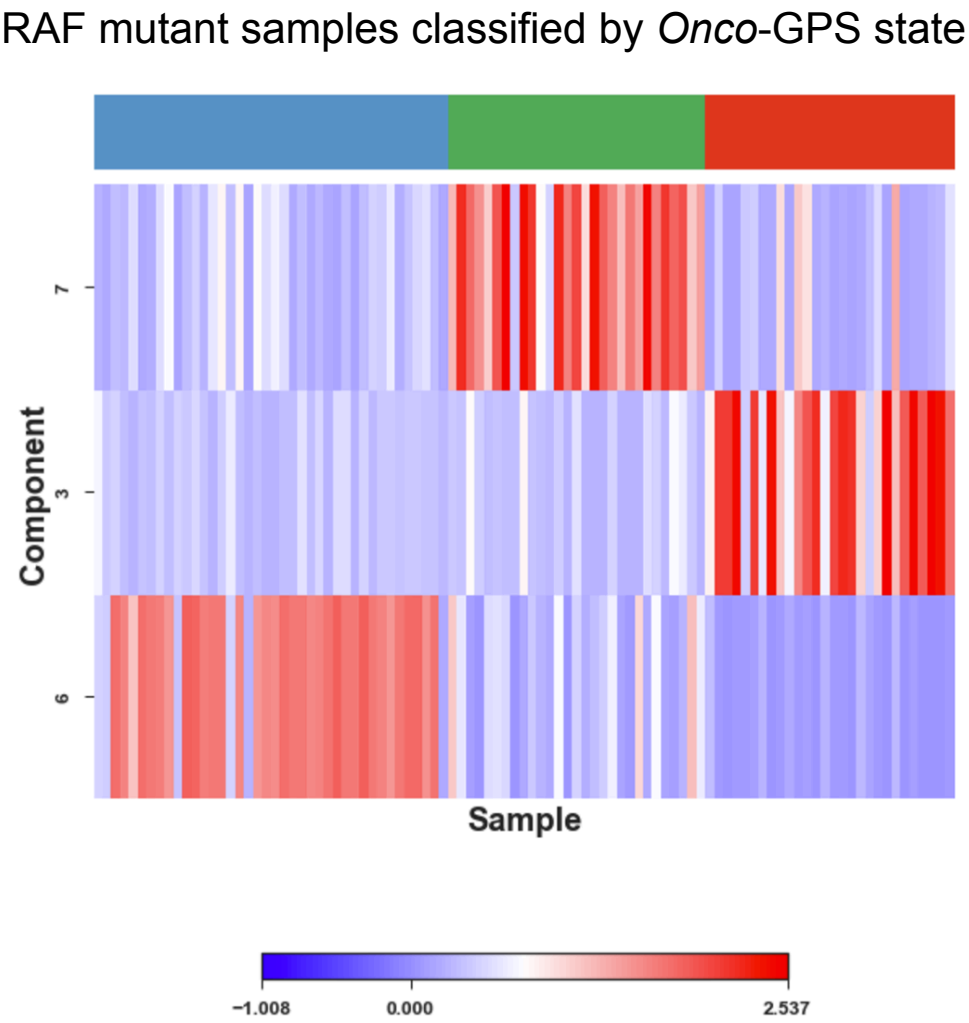

Figure S11. **Related to main Figure 7**. Profile of components *C6*, *C7* and *C3* in the *BRAF* mutant samples. The color phenotypes correspond to the *Onco*-GPS states *S1*-*S3*.

Figure S12

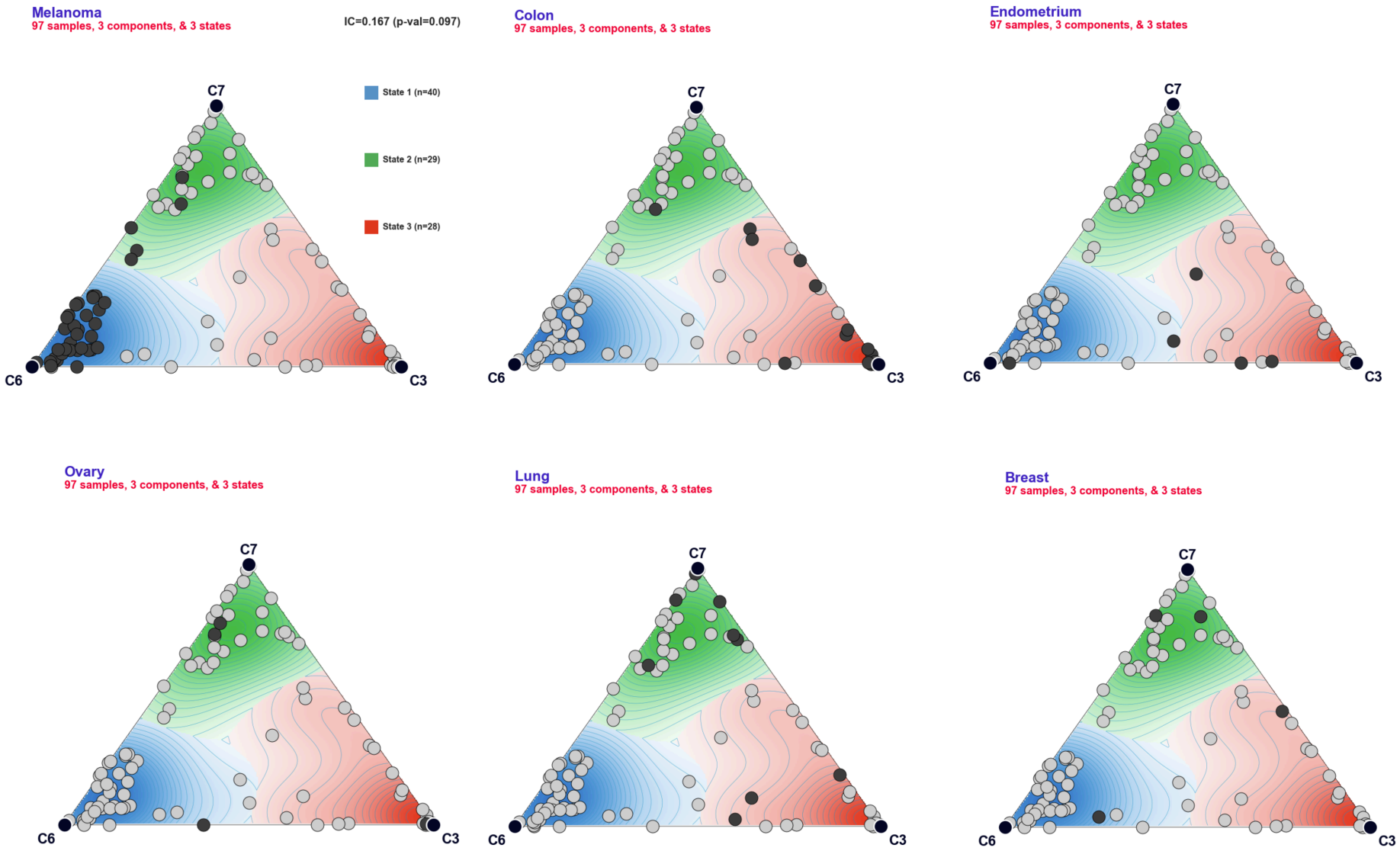

Figure S12. Related to main Figure 7. Tissue representation of BRAF mutant cancers across 3 cell states in the BRAF Onco-GPS map.

Figure S13

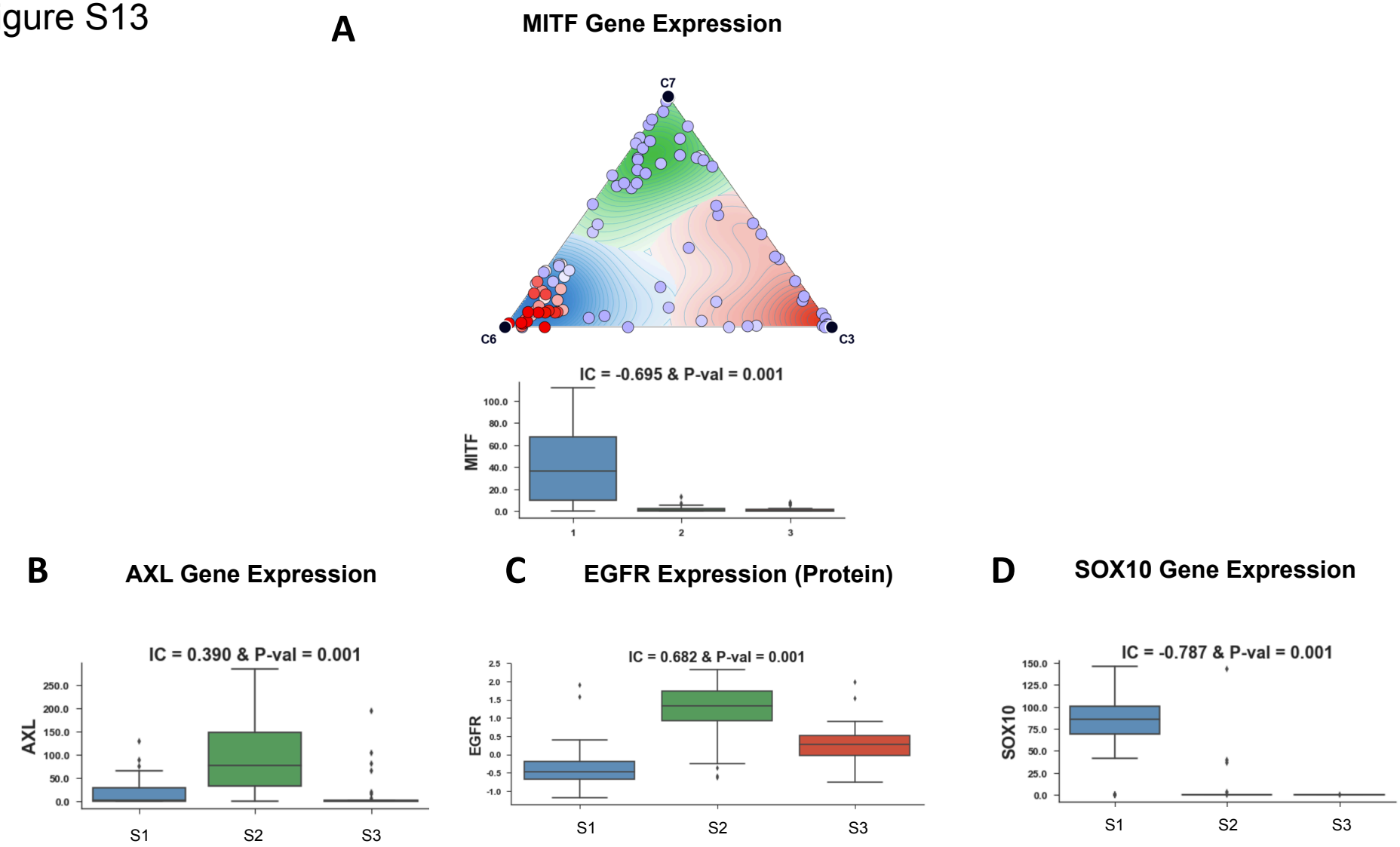

Figure S13. **Related to main Figure 7.** A) Gene expression of MITF across the *BRAF* mutants *Onco*-GPS states. Selected RTK's in the same *Onco*-GPS: B) AXL expression, C) EGFR (protein) and D) SOX10 expression.

Figure S14

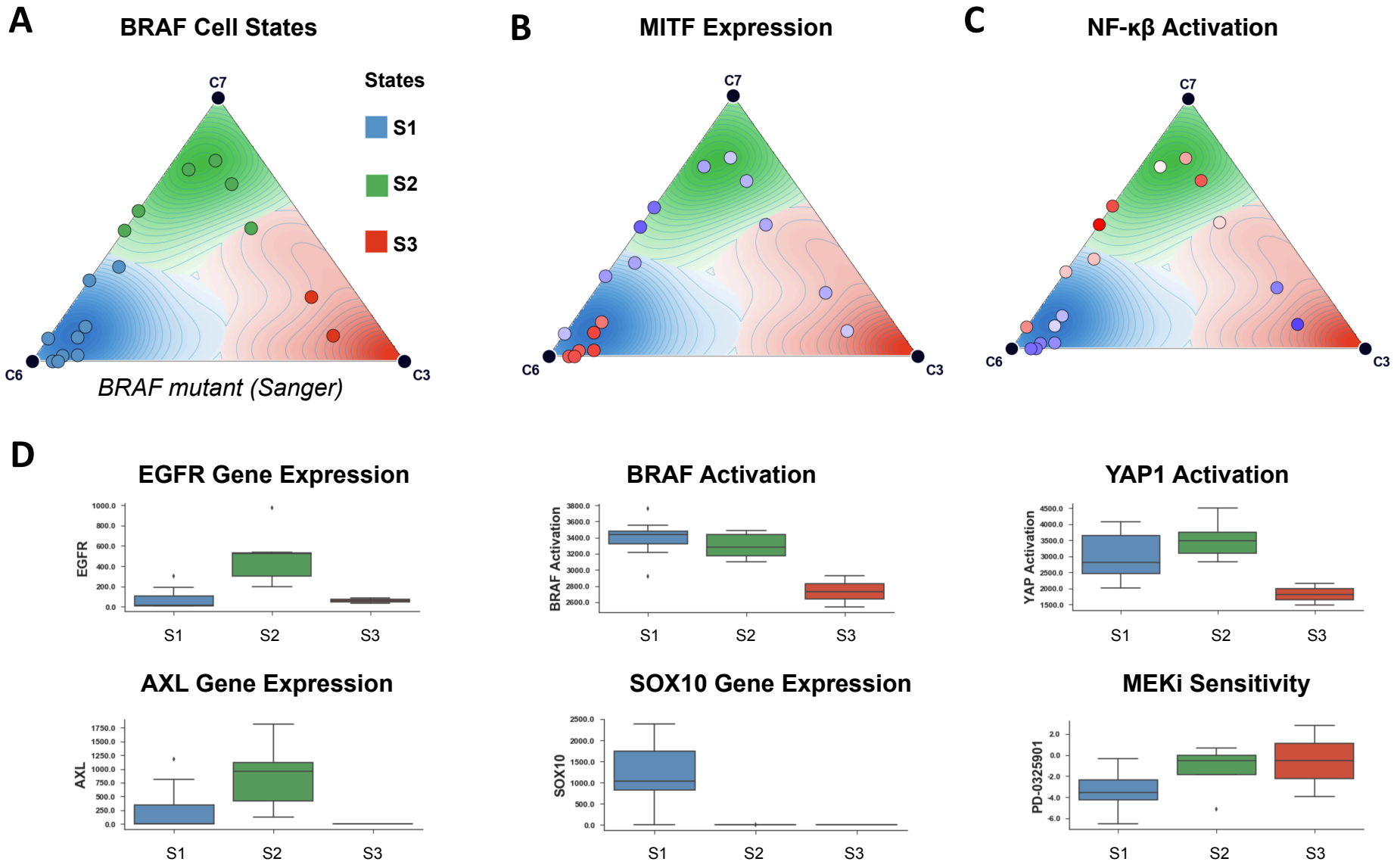

Figure S14. Related to main Figure 7. A) Projection of *BRAF* mutant non-overlapping samples in the Sanger dataset on top of the BRAF *Onco*-GPS. B) Expression of MITF, C) NF-κB and D) selected RTK's display the same patterns as in the CCLE dataset.

Figure S15

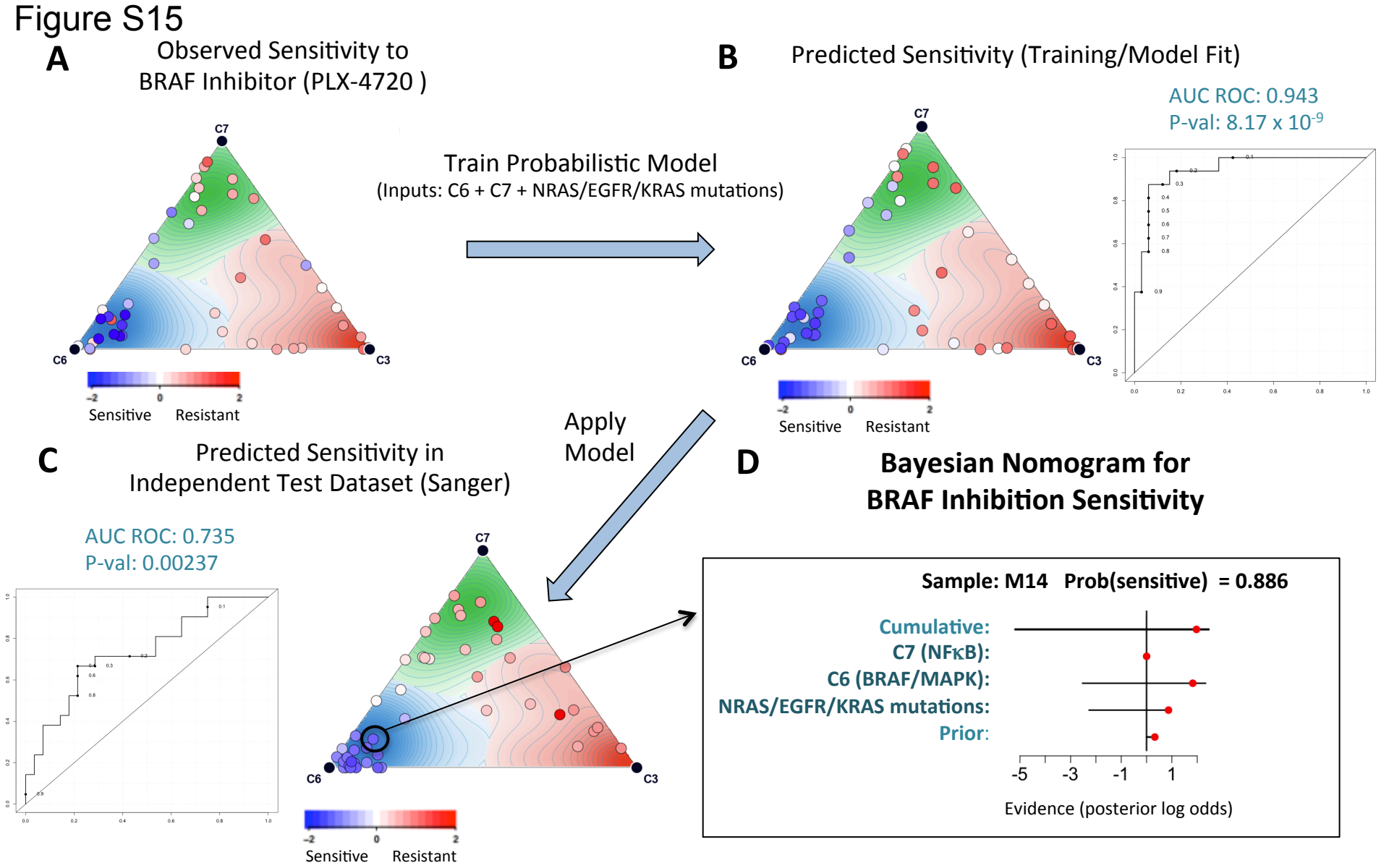

Figure S15. Related to main Figure 7. Probabilistic model for predicting BRAF inhibition: A) BRAF *Onco*-GPS showing observed sensitivity to the PLX-4720 BRAF inhibitor. B) Prediction/ROC curve (model fit) of samples in the training set. C) Prediction/ROC curve for samples in an independent test dataset (Sanger), and D) Bayesian nomogram showing an individual sample's prediction and the weight of evidence from each of the model inputs: *C6*, *C7* and *NRAS/EGFR/KRAS* mutation status.

Figure S16

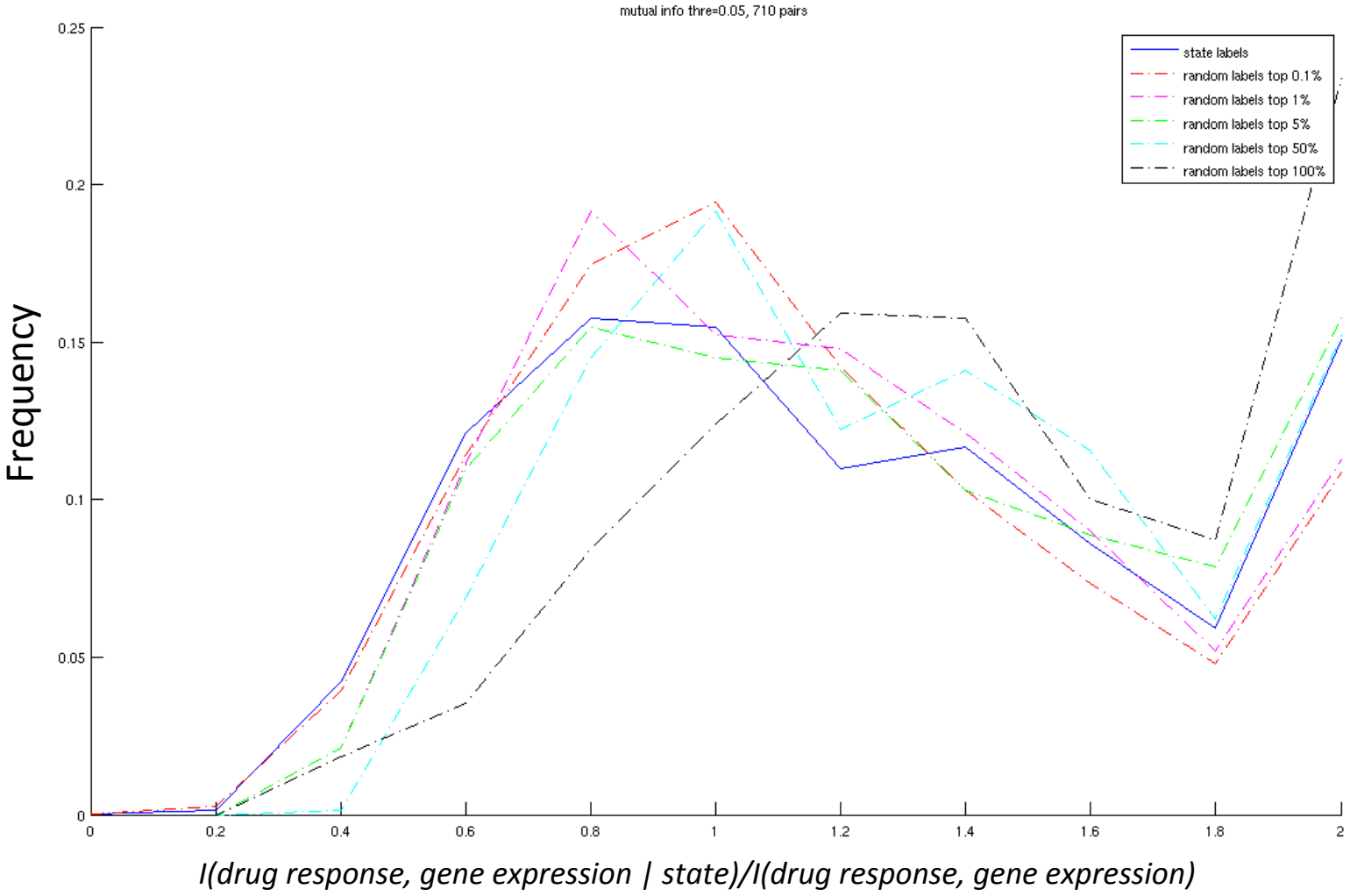

Figure S16. **Related to main Figure 7.** Observed and randomly permuted data distributions of *NCMI* scores for gene expression-drug response pairs whose mutual information is equal or greater than 0.05.

Figure S17

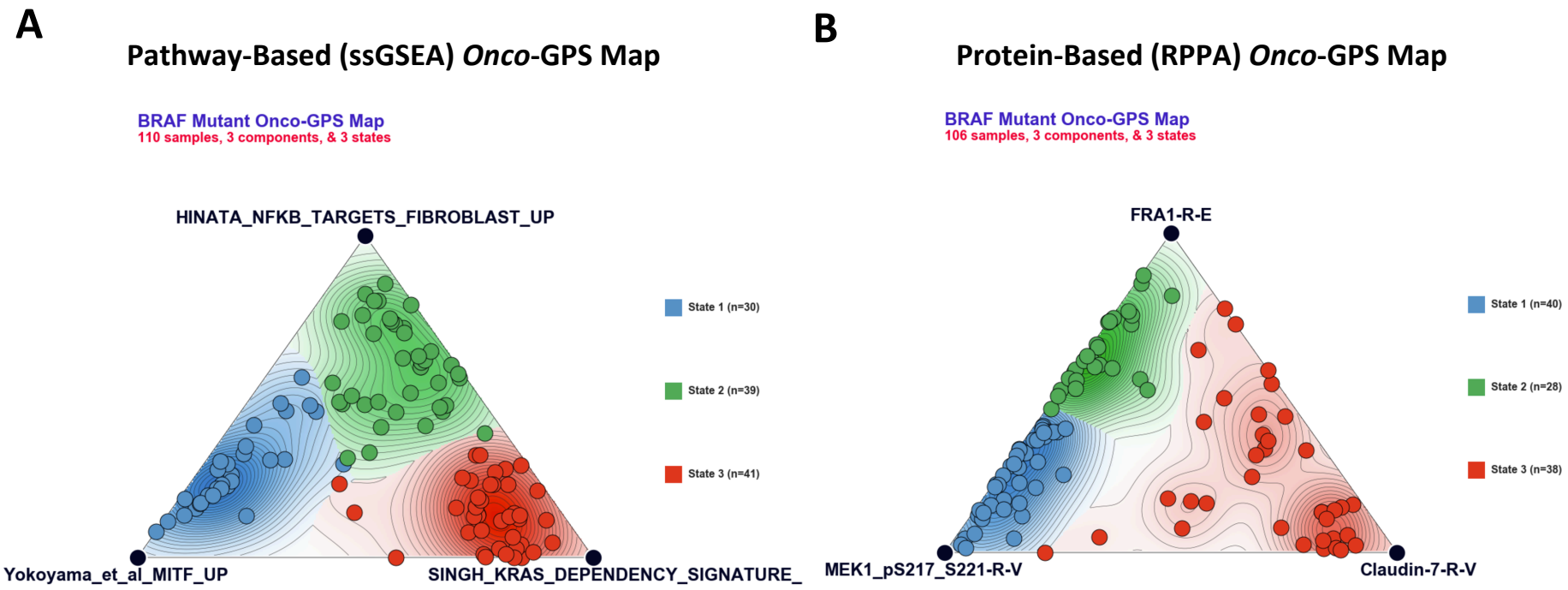

Figure S17. Related to main Figure 7. *BRAF* mutant *Onco*-GPS maps generated using as nodes: A) three single-sample GSEA scores of relevant gene sets, and B) three RPPA relevant protein profiles.