Supplementary Figures

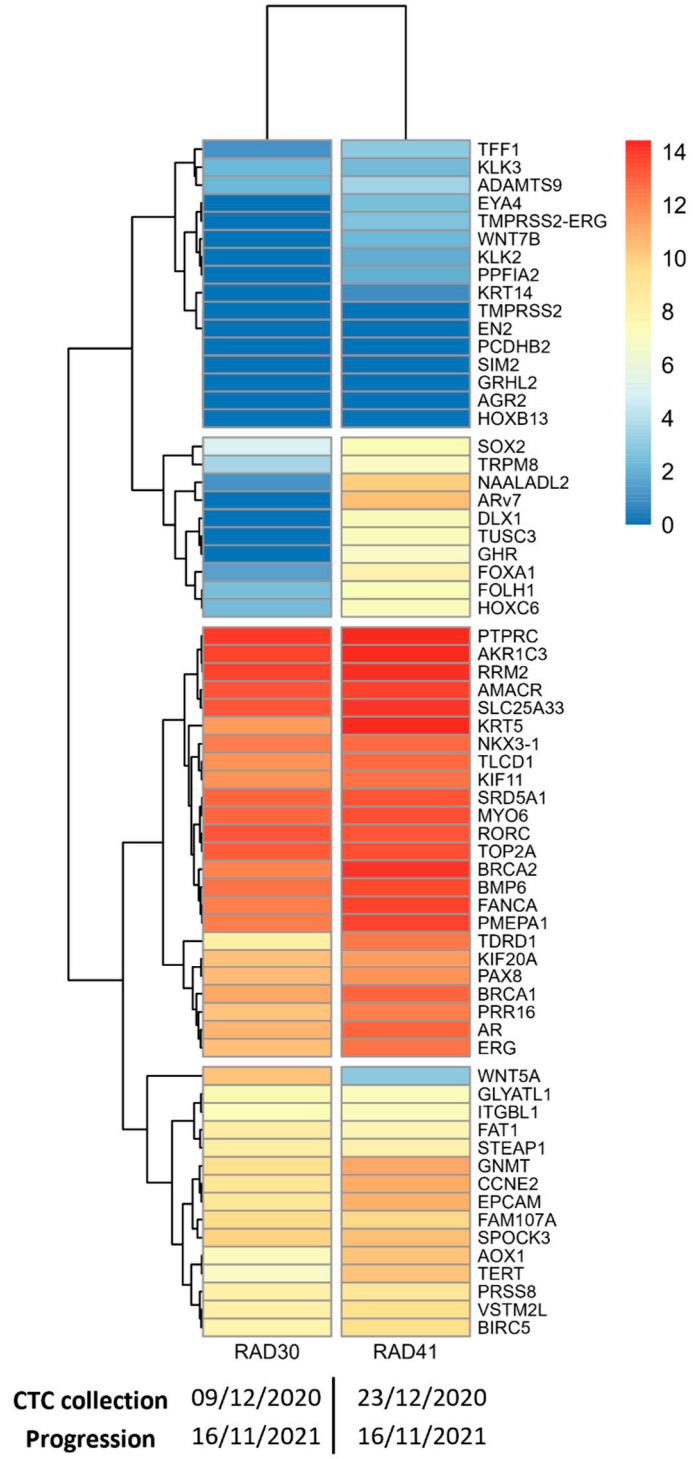

Figure S1) CTC profiles of samples 'RAD30' and 'RAD41' based on the complete gene panel. Samples were collected from a patient receiving PARPi, 'RAD30' at baseline followed by 'RAD41' 14 days later. Expression annotation: log2 expression values.

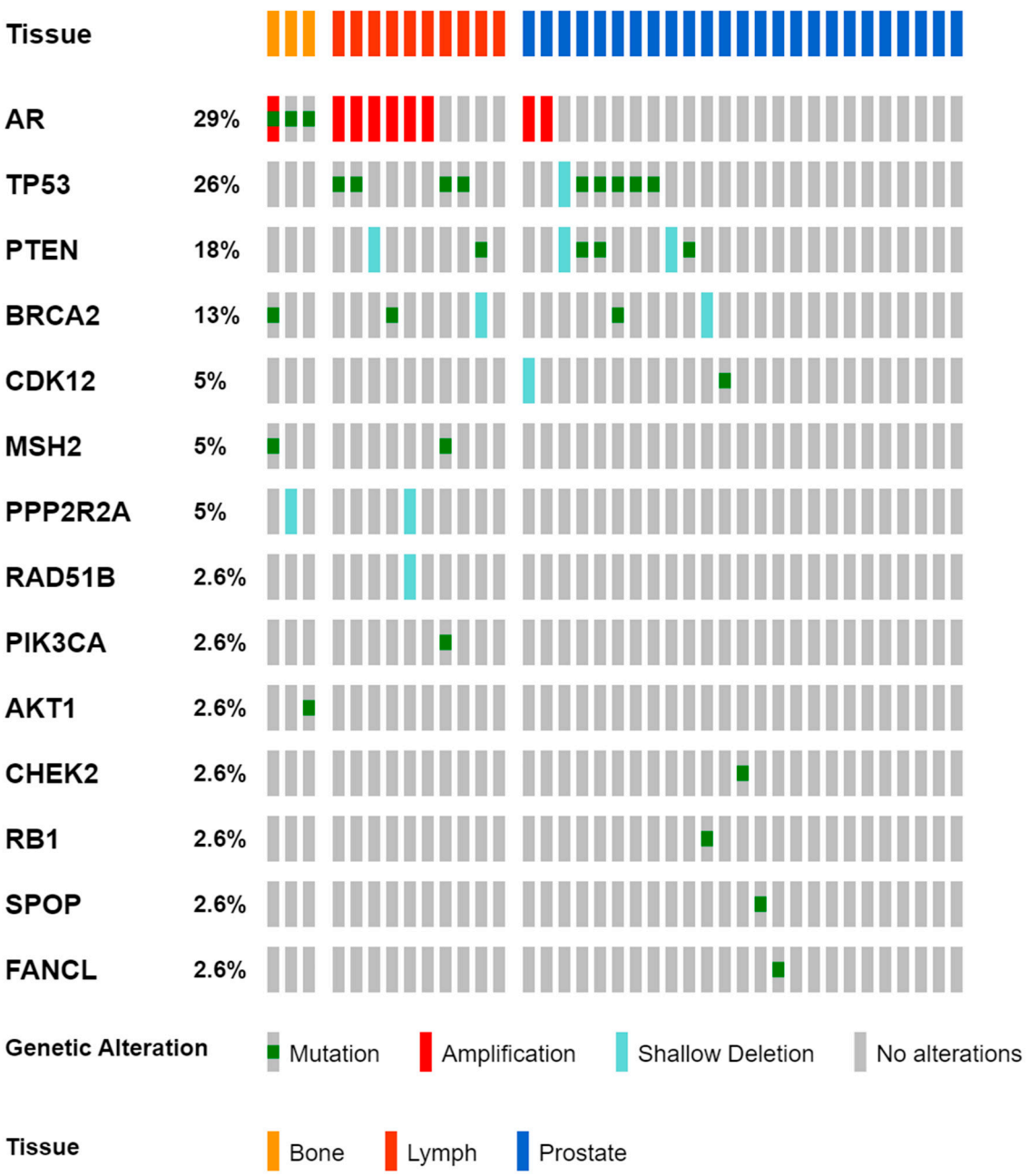

Figure S2) Genetic alterations identified through next generation DNA sequencing in the PROMPT trial. Genetic alterations: Mutation, inframe, missense, splice, or truncal mutations; Amplification, copy number amplification; Shallow Deletion, heterogeneous deletion; No alterations, wildtype. Tissue; Bone, metastatic bone biopsy; Lymph, metastatic lymph-node biopsy; Prostate, prostate tissue biopsy.

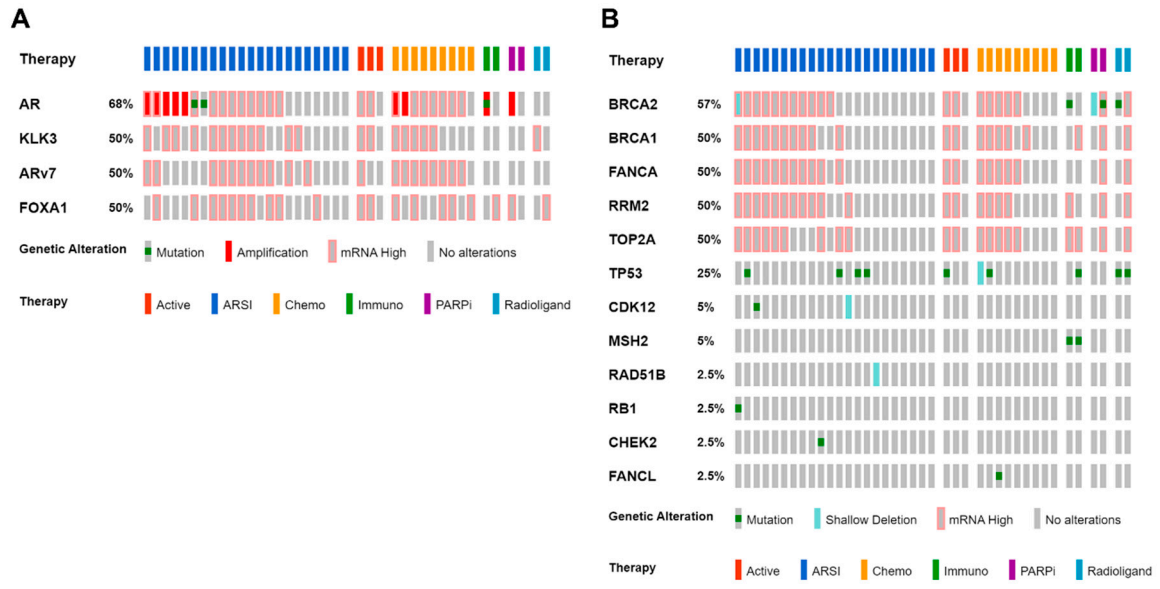

Figure S3) Genetic alterations in tissue biopsies and high gene expression in matched CTC samples of in AR signaling genes (A) and DDR genes (B). Genetic alterations: Mutation, inframe, missense, splice, or truncal mutations in tissue biopsies; Amplification, copy number amplification in tissue biopsies; Shallow Deletion, heterogeneous deletion in tissue biopsies; mRNA High; high expression in CTC samples; No alterations, wildtype gene in tissue biopsies. Therapy; Active, active surveillance; ARSI, ARSI therapy; Chemo, chemotherapy; Immuno, immunotherapy; PARPi, PARPi therapy; Radioligand, radioligand therapy.

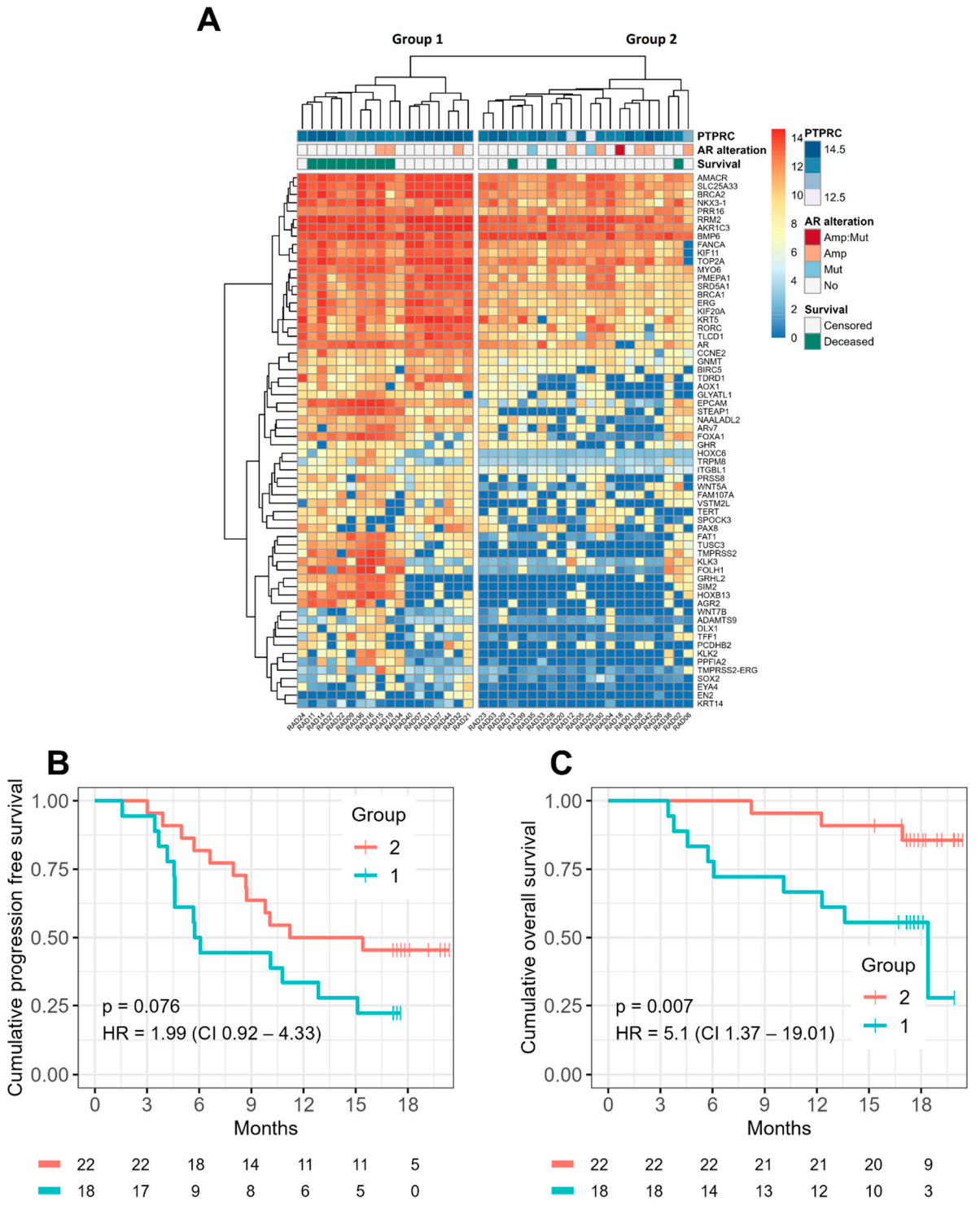

Figure S4) Hierarchical clustering of the therapy-agnostic cohort using the complete gene panel (A). Cluster *p*-values are *p*=0.26 for 'Group 1' and *p*=0.27 for 'Group 2'. PFS (B) and OS (C) of patients with either 'Group 1' and 'Group 2' profiles. Expression annotation: log2 expression values. Heatmap annotation: PTPRC, leukocyte background signal in each sample; AR alteration, Amp:Mut, AR amplification and mutation, Amp, AR amplification, Mut, AR mutation, No, no alteration; Survival, Censored, alive at last follow-up, Deceased, deceased at last follow-up. Survival statistics: HR, Hazard ratio; CI, 95% confidence interval; *p*, *p*-value.

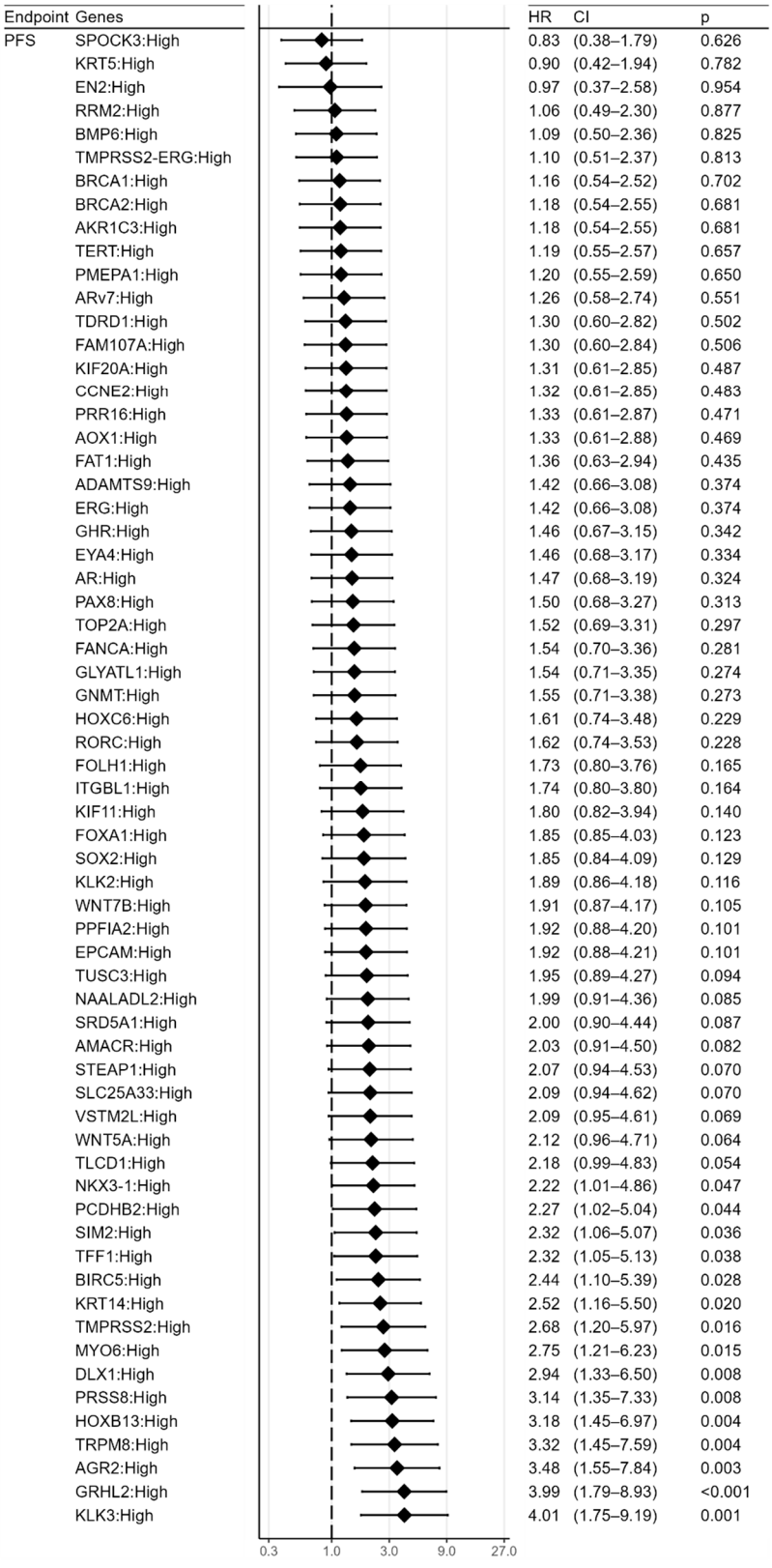

Figure S5) The prognostic value of genes from the complete gene panel on PFS in the therapy-agnostic cohort. A multivariate model was used to determine risk for progression (HR), 95% confidence intervals, and statistical significance (p). Survival statistics: HR, Hazard ratio; CI, Confidence interval; *p*, *p*-value.

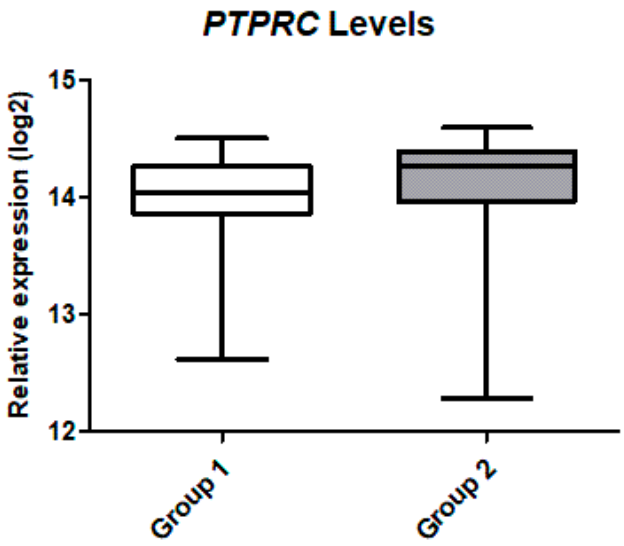

Figure S6) *PTPRC* levels in 'Group 1' (n=16) and 'Group 2' (n=24) patients from therapy-agnostic cohort. Patients were grouped via unsupervised hierarchical clustering using the agnostic gene panel (Figure 2A).

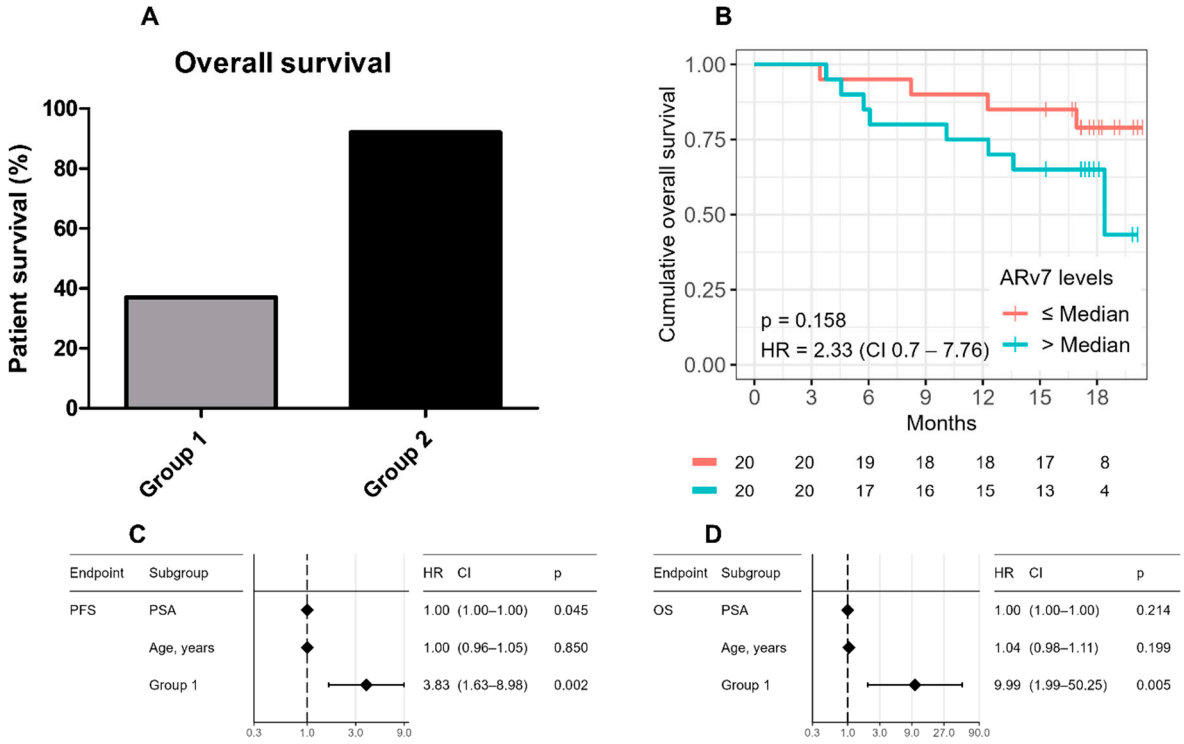

Figure S7) Survival of 'Group 1' (n=16) and 'Group 2' (n=24) patients in the therapy-agnostic cohort at last follow-up (A). The prognostic value of *ARv7* levels on OS in the therapy-agnostic cohort (B). Multivariate analysis on PFS (C) and OS (D) including variables: PSA, age, and the 'Group 1' profile in the therapy-agnostic cohort. Survival statistics: HR, Hazard ratio; CI, 95% Confidence interval; *p*, *p*-value.

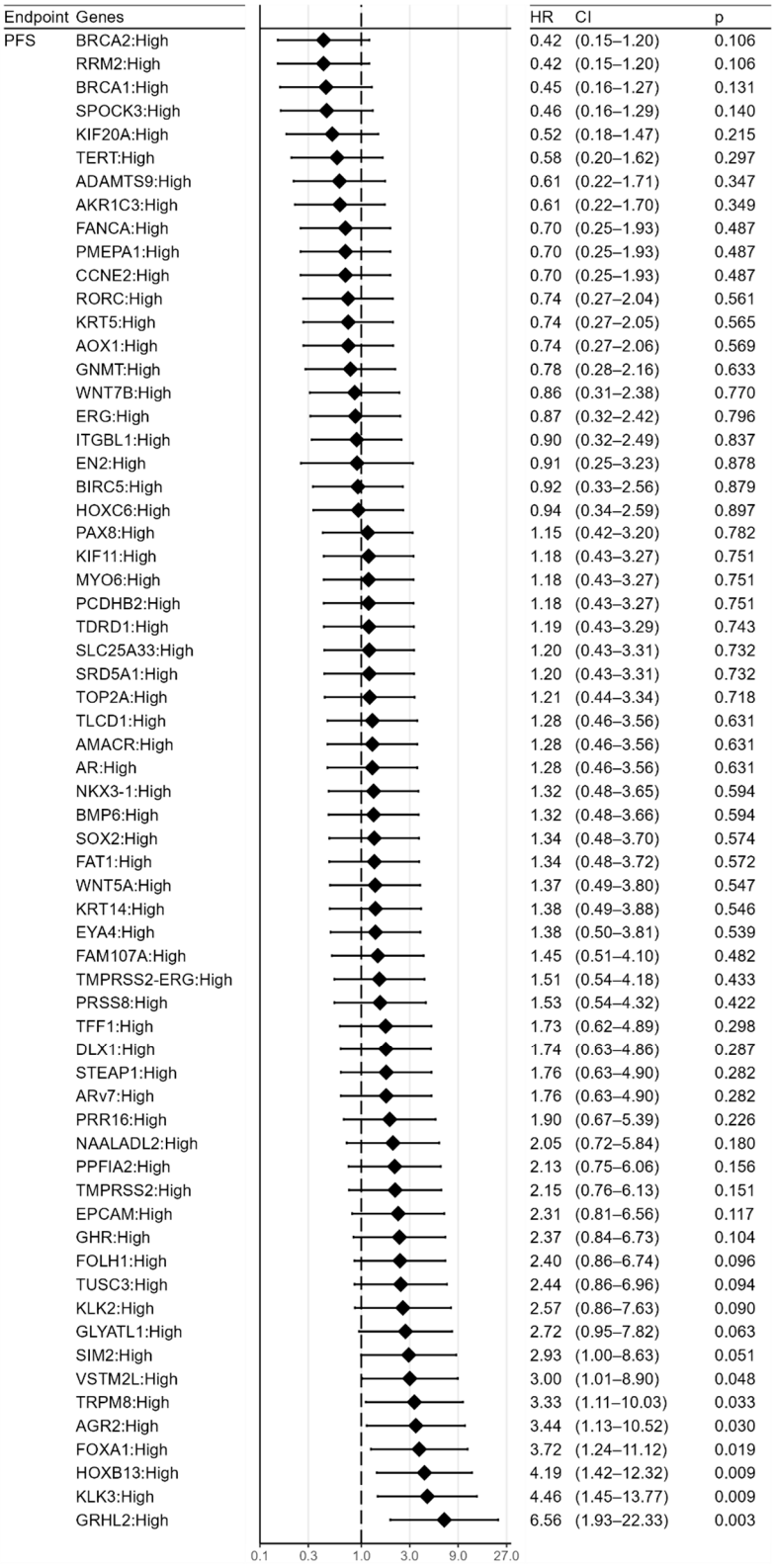

Figure S8) The prognostic value of genes from the complete gene panel on PFS in the ARSI cohort. A multivariate model was used to determine risk for progression (HR), 95% confidence intervals, and statistical significance (p). Survival statistics: HR, Hazard ratio; CI, Confidence interval; *p*, *p*-value.

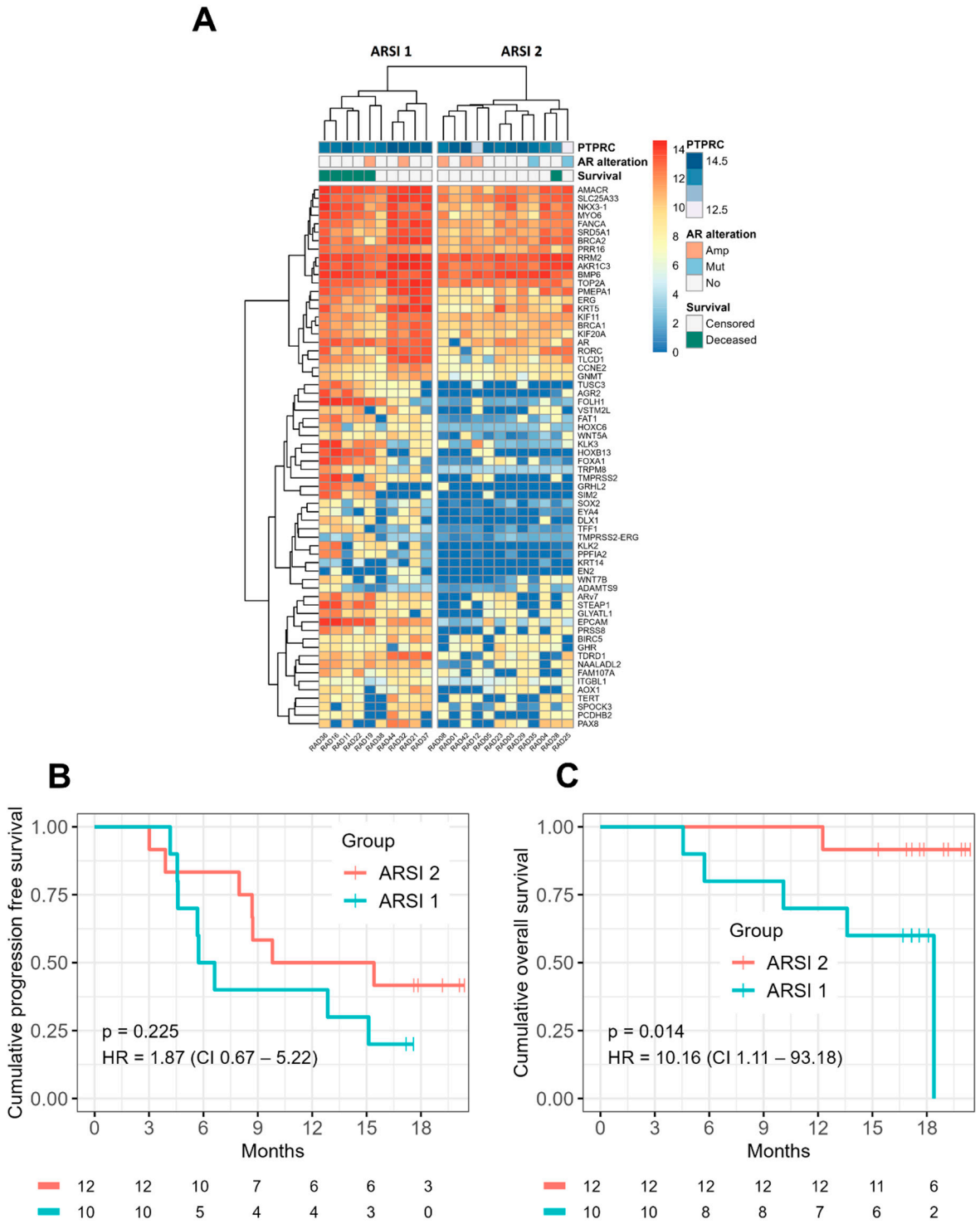

Figure S9) Hierarchical clustering of the ARSI cohort using the complete gene panel (A). Cluster *p*-values are *p*=0.26 for 'ARSI 1' and *p*=0.3 for 'ARSI 2'. Kaplan-Meier plots showing PFS (B) and OS (C) of patients with 'ARSI 1' and 'ARSI 2' profiles. Expression annotation: expression is shown in log2 values, from 0 (dark blue) to 14 (deep red). Heatmap annotations: PTPRC, leukocyte background signal in each sample; AR alteration, Amp, AR amplification, Mut, AR mutation, No, no alteration; Survival, Censored, alive at last follow-up (white), Deceased, deceased at last follow-up survey (green). Survival statistics: HR, Hazard ratio; CI, 95% confidence interval; *p*, *p*-value.

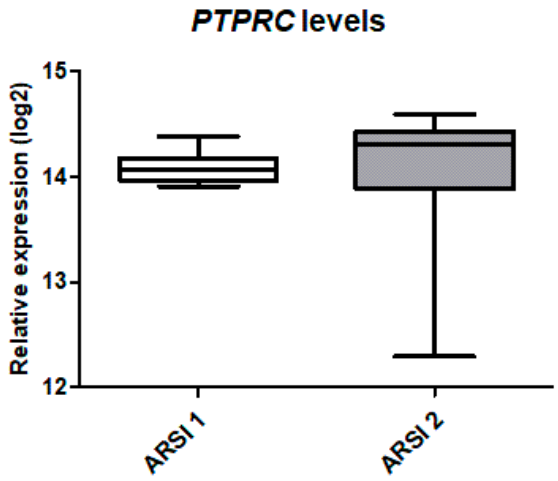

Figure S10) *PTPRC* levels in 'ARSI 1' and 'ARSI 2' patients. Patients were grouped via unsupervised hierarchical clustering using the ARSI gene panel (Fig. 3A).

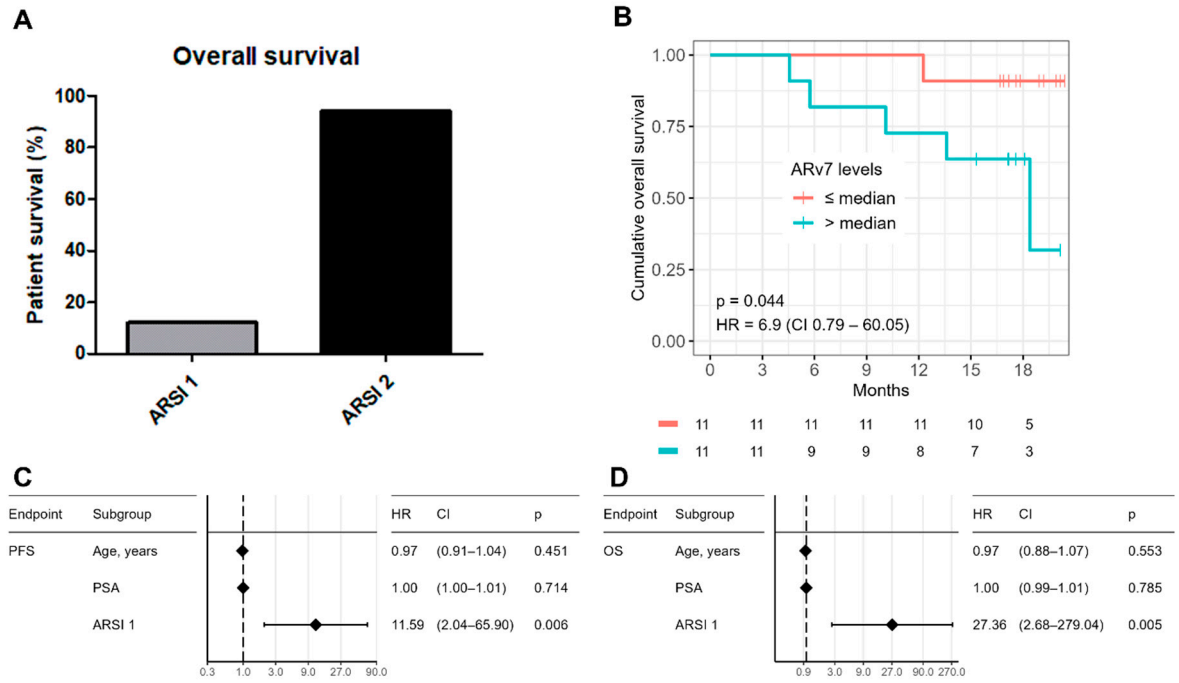

Figure S11) Survival of 'ARSI 1' and 'ARSI 2' patients in the ARSI cohort at last follow-up (A). The prognostic value of *ARv7* levels on OS in the ARSI cohort (B). Multivariate analysis on PFS (C) and OS (D) including variables: PSA, age, and the 'ARSI 1' profile in the ARSI cohort. Survival statistics; HR, Hazard ratio; CI, 95% confidence interval; *p*, *p*-value.

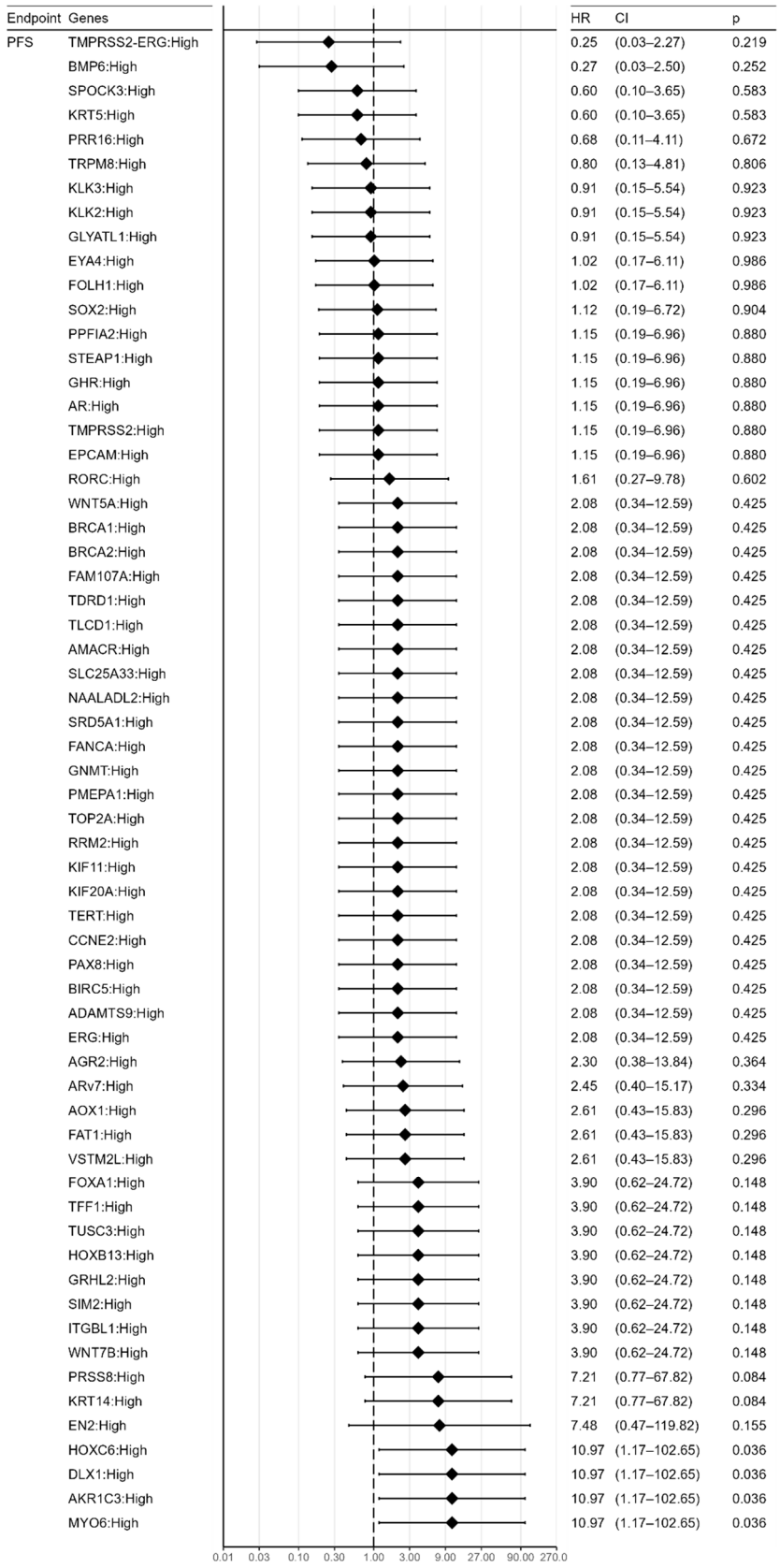

Figure S12) The prognostic value of genes in the complete gene panel on PFS in the chemotherapy cohort. A multivariate model was used to determine risk for progression (HR), 95% confidence intervals, and statistical significance (*p*). Survival statistics: HR, Hazard ratio; CI, Confidence interval; *p*, *p*-value.