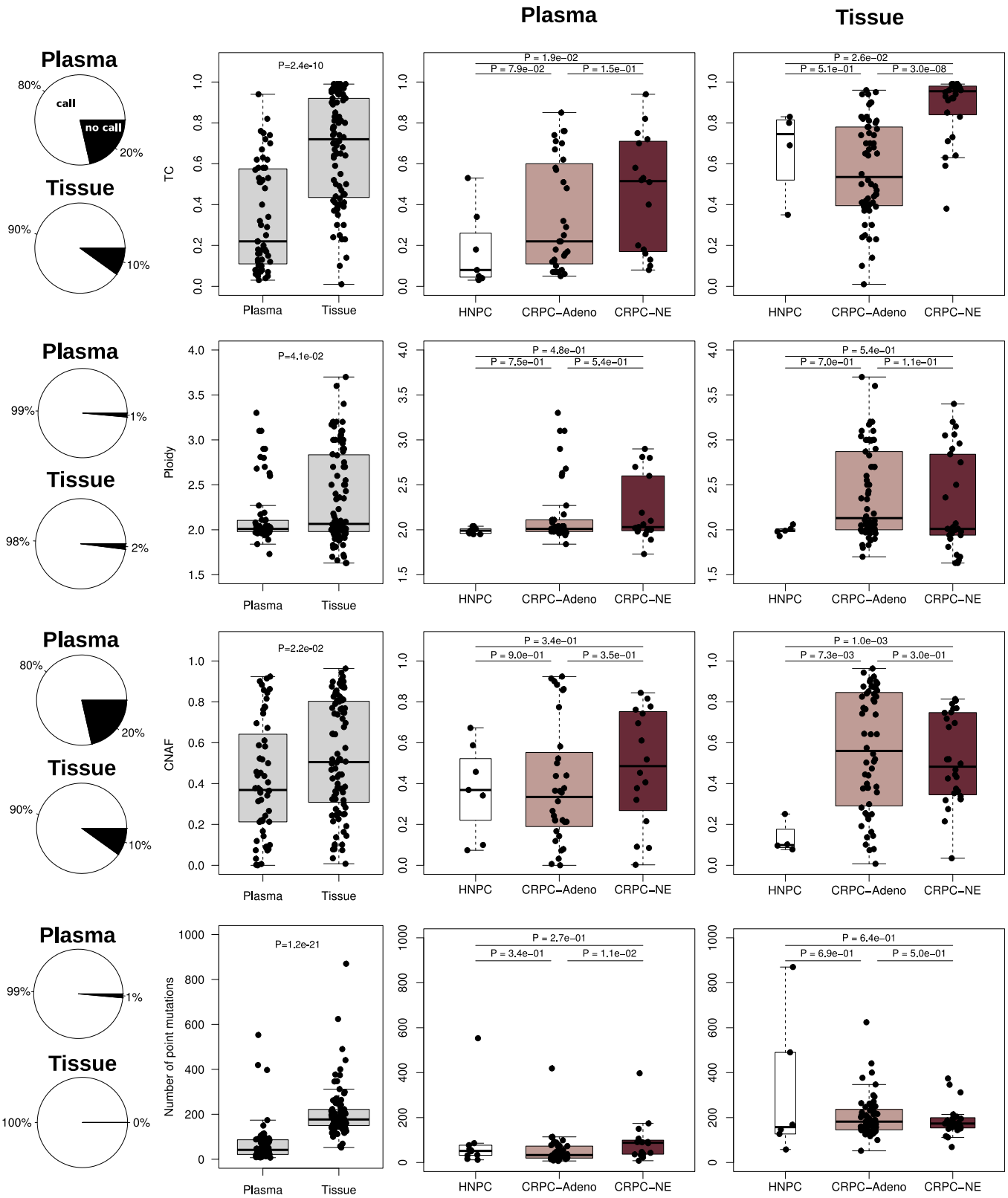
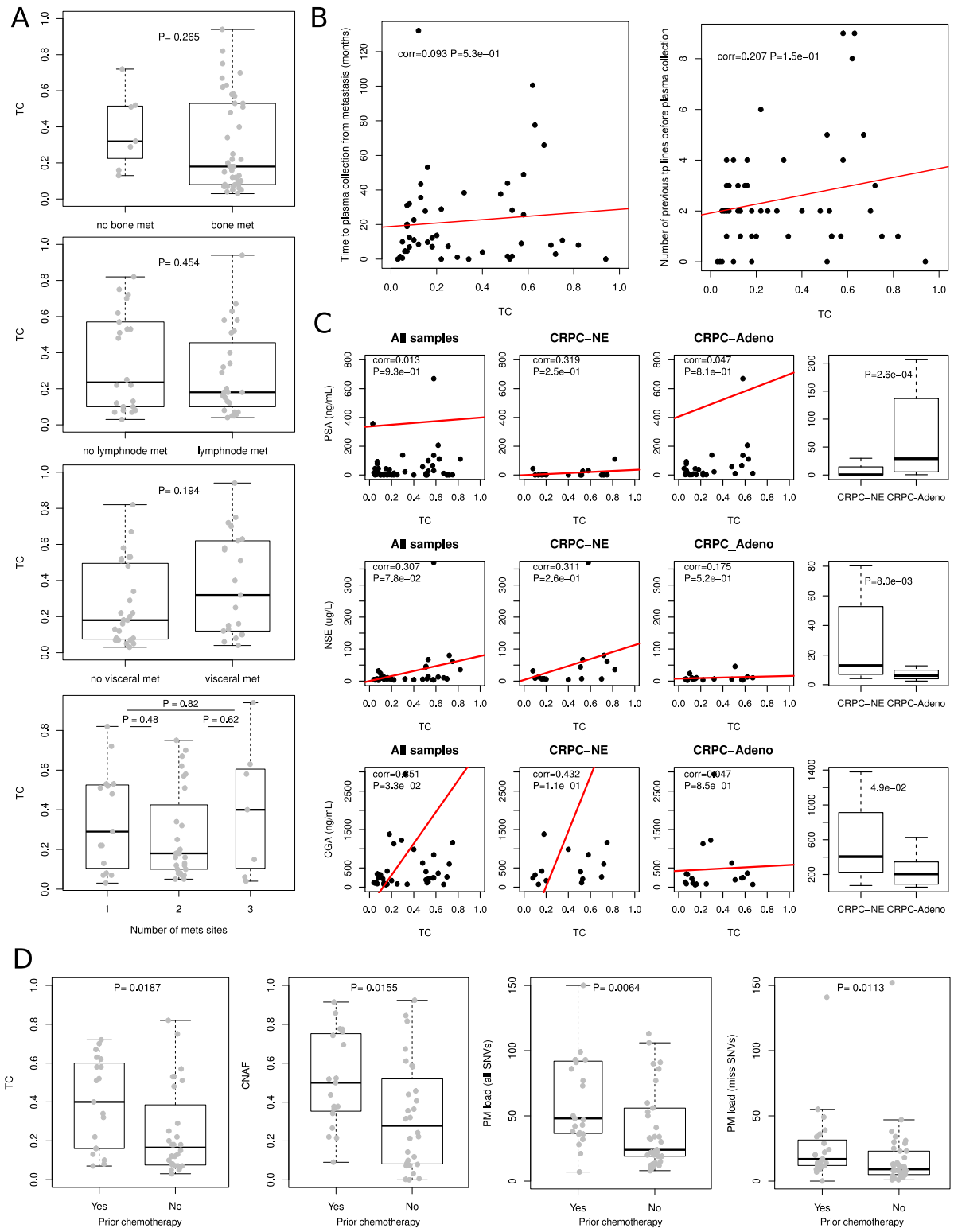
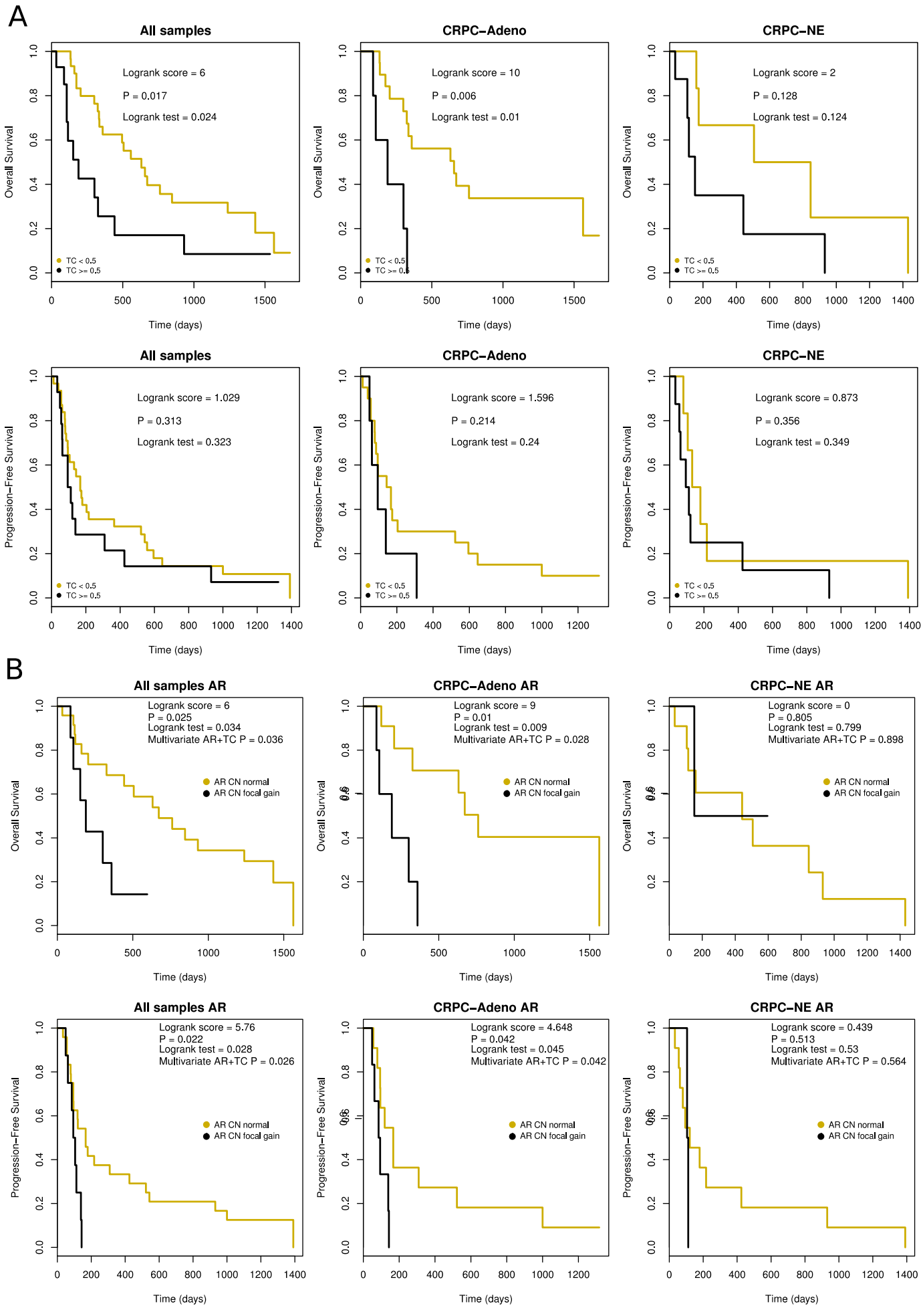
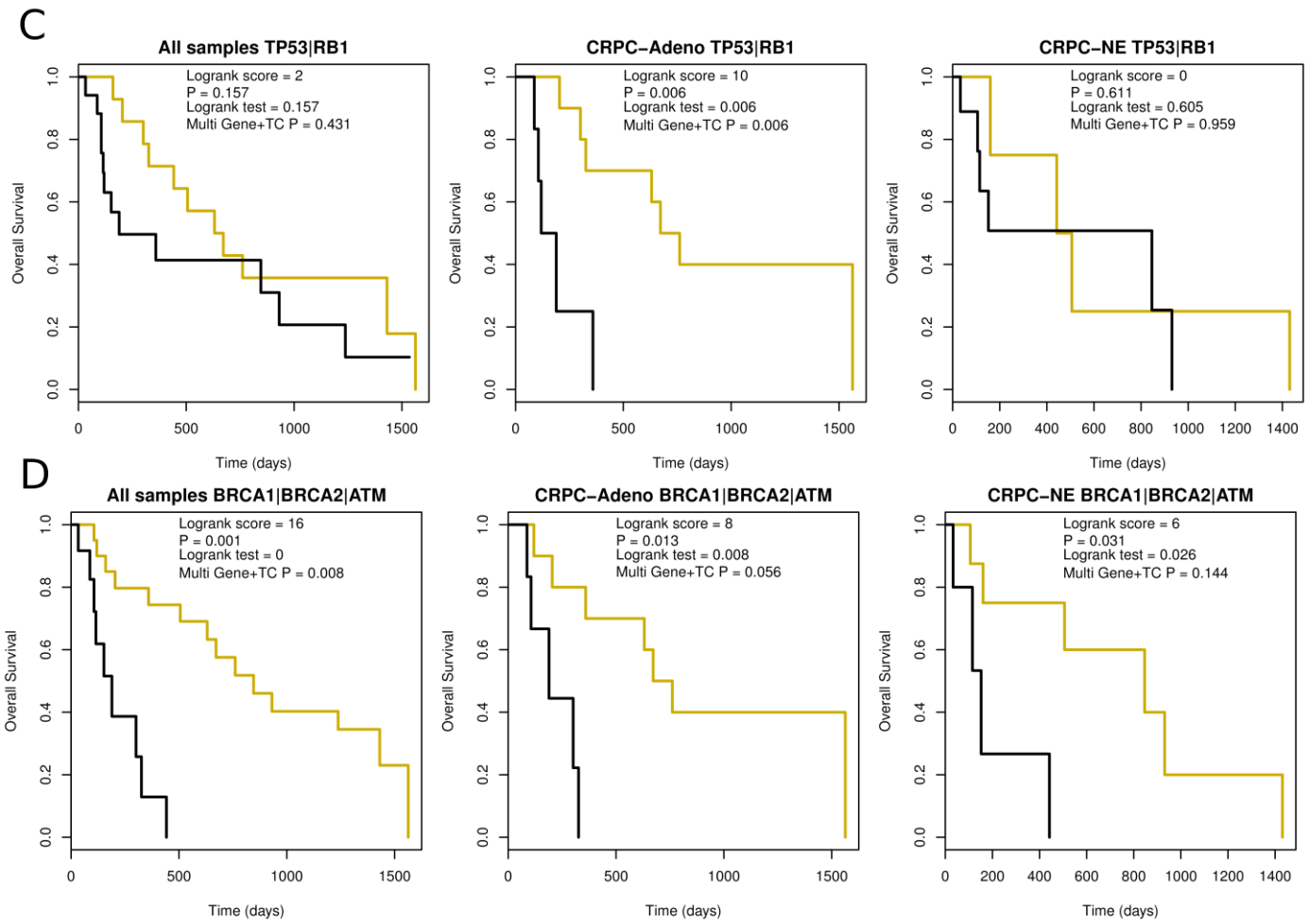


Supplementary Figure 1. Distribution of tumor content (TC), tumor ploidy, copy number aberration fraction (CNAF) and total number of somatic SNVs computed from genomic data across plasma and tumor tissue samples and across sample types. Reported p-values are computed using two-tailed Wilcoxon-Mann-Whitney test. Pie-charts represent for each genomic variable the fraction of samples for which we were able to estimate (white portion) the value among, respectively, plasma and tissue samples.

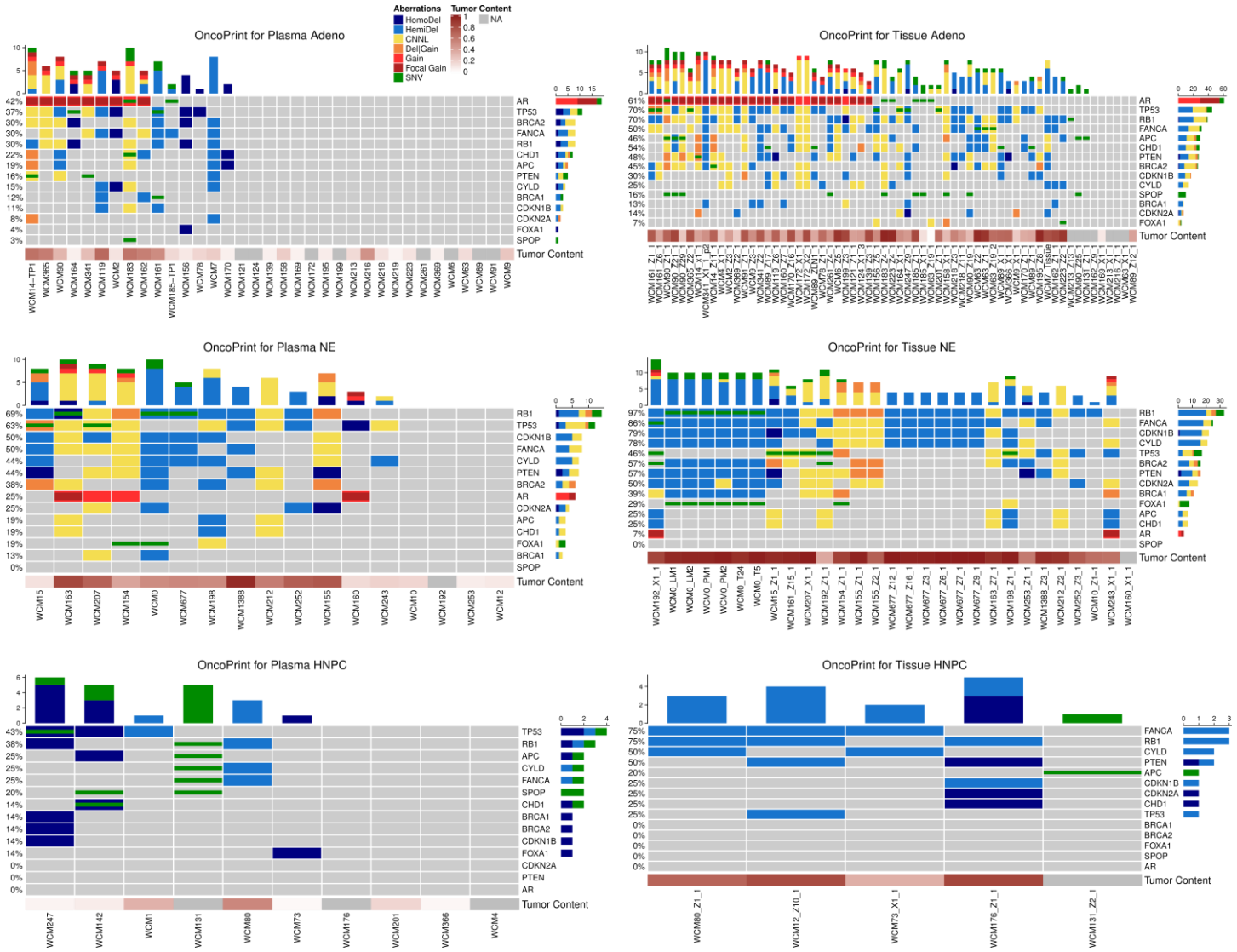


Supplementary Figure 2. Analysis of plasma genomics and clinical variable associations. A) Distribution of tumor content (TC) estimation in plasma among patients with different type and number of metastasis type. B) Correlation of TC estimations in plasma and time to plasma collection from metastasis and number of therapy lines before plasma collection. C) Correlation of TC estimations in plasma and NEPC clinical markers (PSA = prostate specific antigen, NSE = neuron-specific enolase, CGA = chromogranin A) and distribution of NEPC markers across patient's class at plasma collection. D) Distribution of TC, copy number aberration fraction (CNAF), number of SNVs (outliers not shown) and number of missense SNVs (outliers not shown) across patients with or without chemotherapy treatment prior to plasma collection. Reported p-values are computed using two-tailed Wilcoxon-Mann-Whitney test or Pearson correlation.

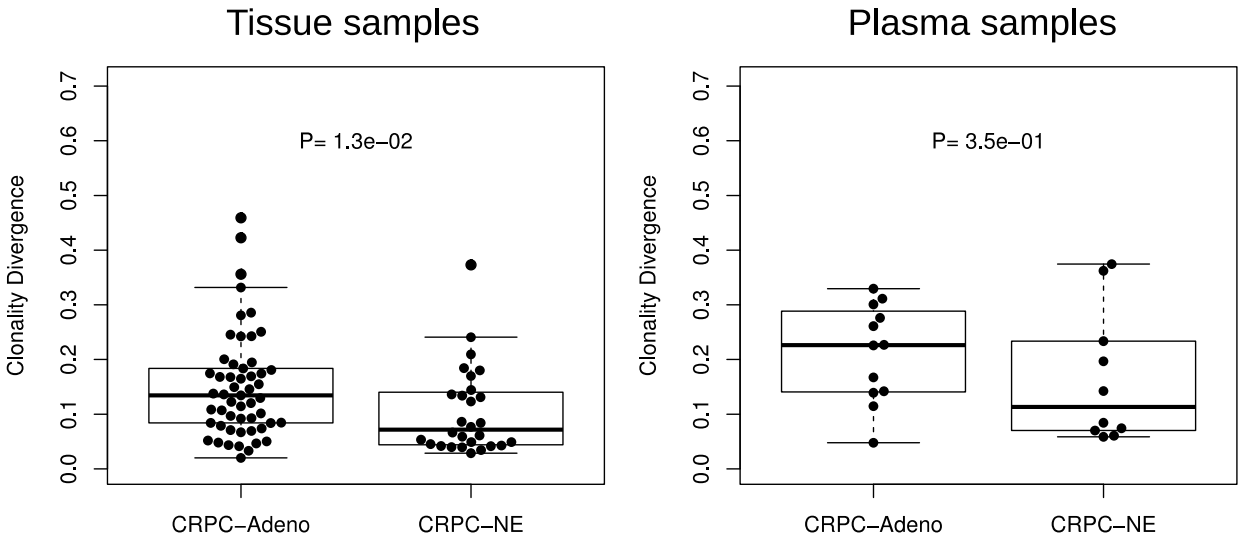

A
All samples
Logrank score = 6
P = 0.017
Logrank test = 0.024
CRPC−Adeno
Logrank score = 10
P = 0.006
Logrank test = 0.01
CRPC−NE
Logrank score = 2
P = 0.128
Logrank test = 0.124
All samples
Logrank score = 1.029
P = 0.313
Logrank test = 0.323
CRPC−Adeno
Logrank score = 1.596
P = 0.214
Logrank test = 0.24
CRPC−NE
Logrank score = 0.873
P = 0.356
Logrank test = 0.349
Overall Survival
Progression−Free Survival
Time (days)
TC < 0.5
TC >= 0.5
B
All samples AR
Logrank score = 6
P = 0.025
Logrank test = 0.034
Multivariate AR+TC P = 0.036
CRPC−Adeno AR
Logrank score = 9
P = 0.01
Logrank test = 0.009
Multivariate AR+TC P = 0.028
CRPC−NE AR
Logrank score = 0
P = 0.805
Logrank test = 0.799
Multivariate AR+TC P = 0.898
All samples AR
Logrank score = 5.76
P = 0.022
Logrank test = 0.028
Multivariate AR+TC P = 0.026
CRPC−Adeno AR
Logrank score = 4.648
P = 0.042
Logrank test = 0.045
Multivariate AR+TC P = 0.042
CRPC−NE AR
Logrank score = 0.439
P = 0.513
Logrank test = 0.53
Multivariate AR+TC P = 0.564
AR CN normal
AR CN focal gain



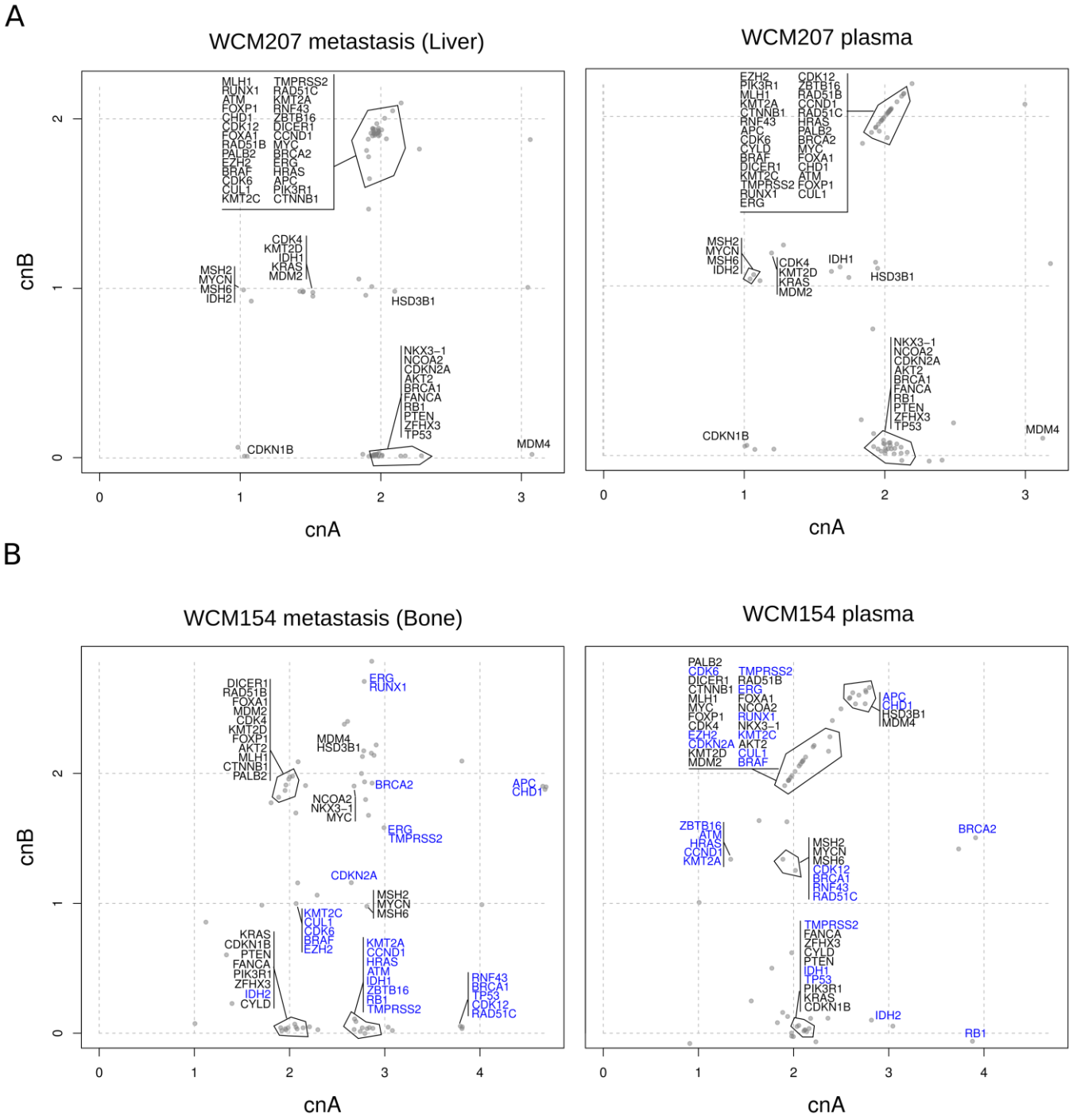
Supplementary Figure 3. Association of plasma tumor content and plasma prostate cancer driver genes with overall survival and progression-free survival. Overall survival and radiographic progression-free survival for A) high versus low tumor content (TC) estimations and for B) *AR* CN neutral versus *AR* focal gain; univariate analysis results only and multivariate (controlling for TC) analysis are shown in the inset. Overall survival for lesions in TP53 and/or RB1 and for BRCA1, BRCA2, ATM; univariate and multivariate analysis are shown in the insets. All analyses are reported for the entire cohort (left), for CRPC-Adeno (center) and for CRPC-NE (right). Univariate overall survival and progression-free survival analyses were performed using the Kaplan-Meier estimator (log-rank test). Multivariate overall and progression-free survival analyses were performed using a proportional hazard model with stepwise model selection by Akaike information criterion using forward and backward directions.



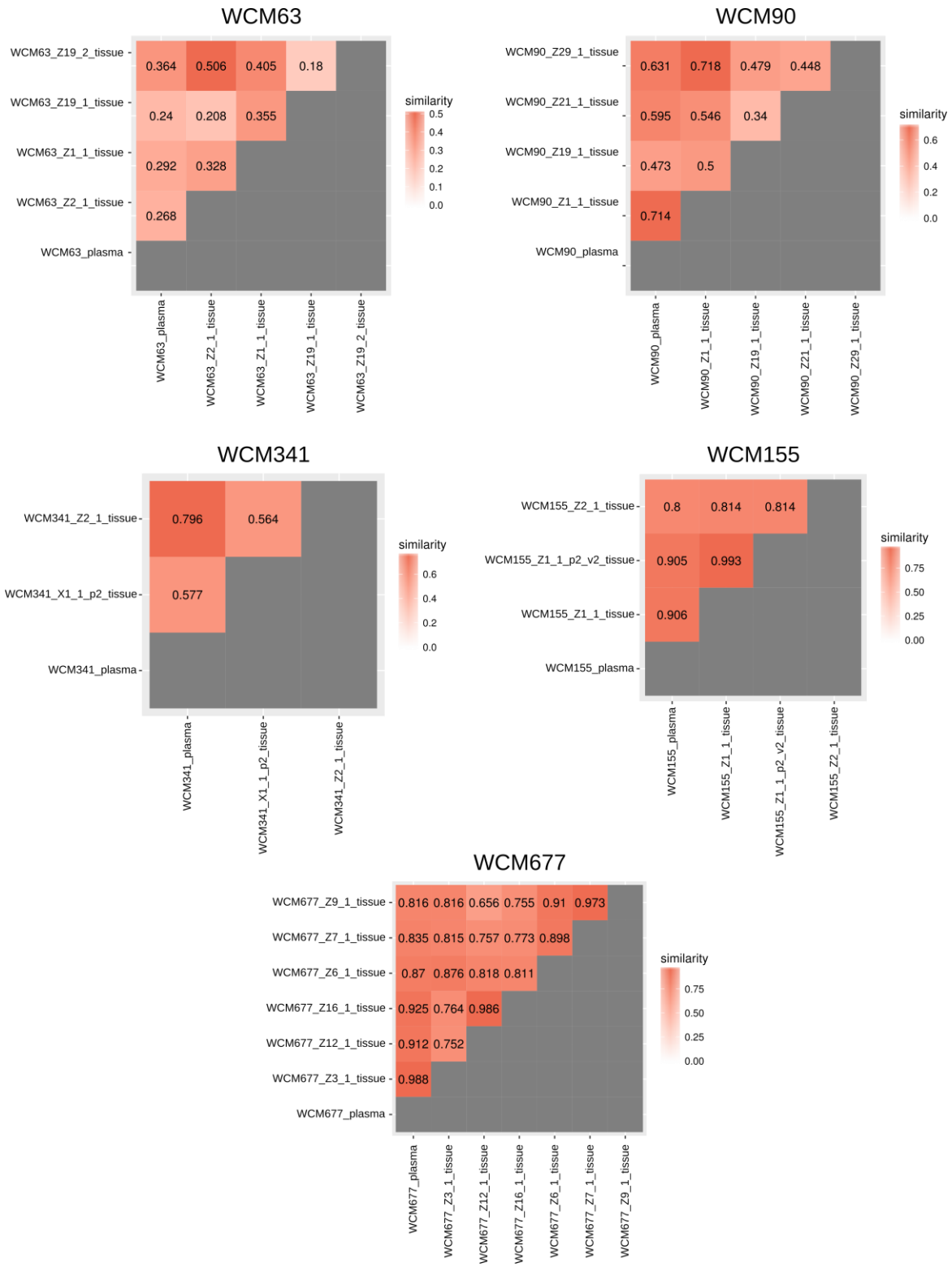
Supplementary Figure 4. Landscape of somatic aberrations in plasma and tissue samples across CRPC-Adeno (top), CRPC-NE (middle), and HNPC (bottom) classes. Grey cells in oncoprints represent either wild-type or absence of available call. Reported gene aberration fractions are computed excluding all samples for which no calls are available neither for SNVs nor for SCNAs.



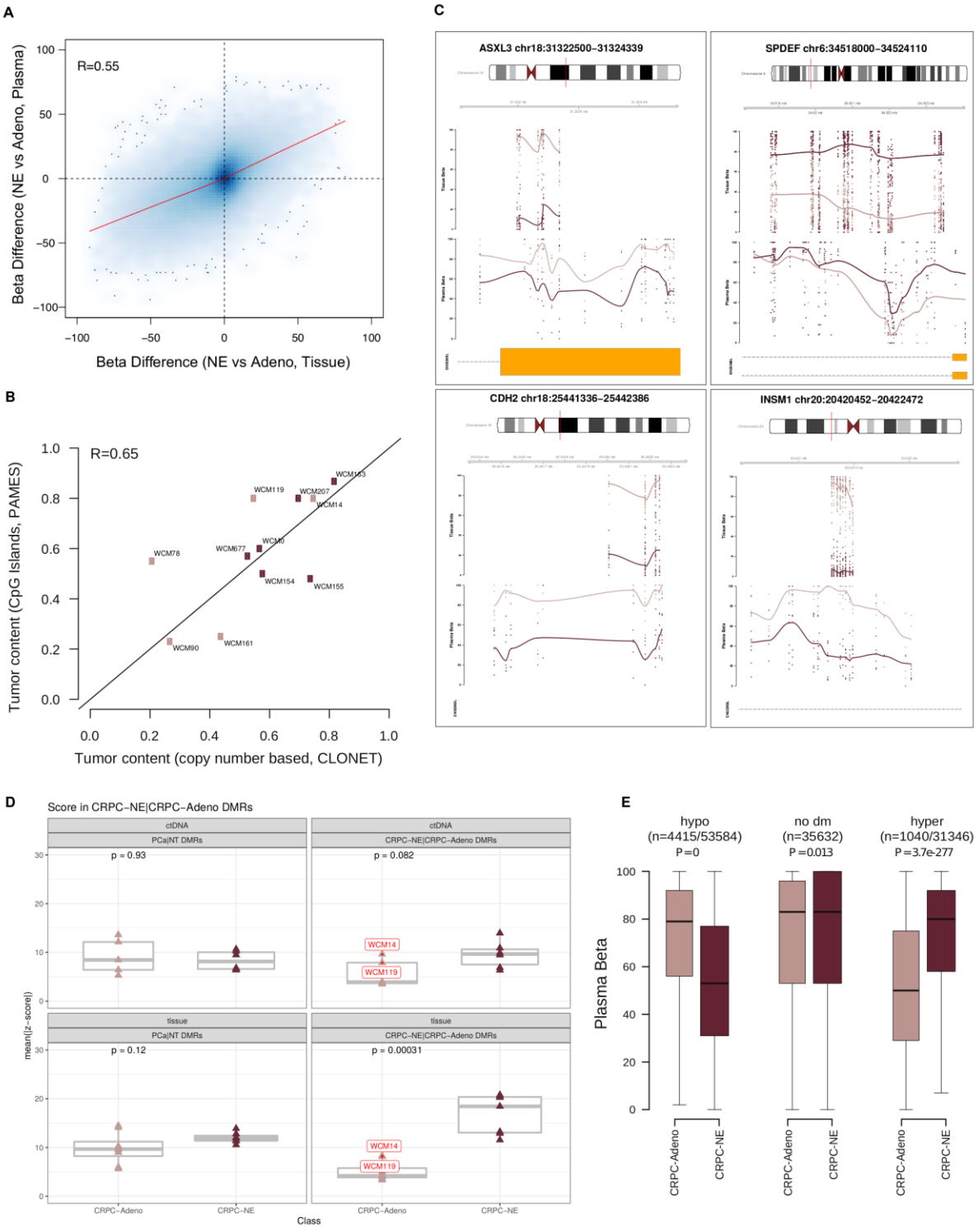
Supplementary Figure 5. Clonality divergence assessed for tissue and plasma study cohort samples. Distribution of the clonality diverge index in tumor tissue and plasma samples across patients classified as CRPC-Adeno and CRPC-NE at plasma collection. Reported p-values are computed using two-tailed Wilcoxon-Mann-Whitney test.



Supplementary Figure 6. A) Example of patient demonstrating almost identical genomic status between a metastasis and a plasma sample, suggesting high homogeneity among all patient's metastases. Polygons include cancer genes with same allele-specific copy number. B) Example of patient with heterogeneous profiles. Blue indicates genes with different allele-specific copy number.

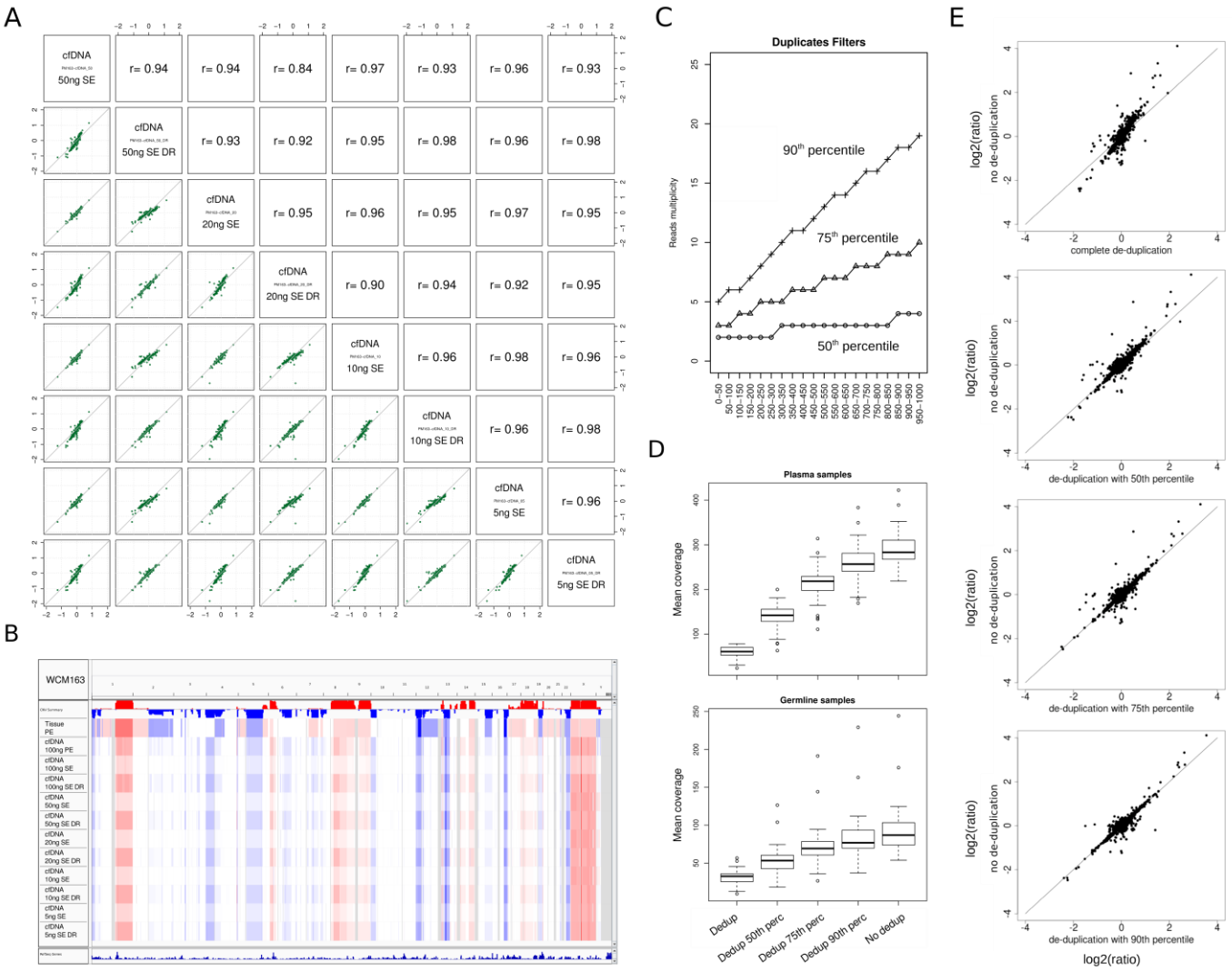


Supplementary Figure 7. SCNAs similarity among plasma and tumor tissue samples of patients with multiple tissue biopsies and plasma tumor content greater or equal than 10%.



Supplementary Figure 8. A) Genome-wide comparison of methylation patterns in CRPC-NE and CRPC-Adeno as measured in plasma and in tissue samples. The differences averaged betas are plotted. Red line shows interpolation by the lowess function; R is the Pearson's correlation coefficient. B) Tumor fraction estimates from patients circulating material. Scatter plot of the tumor purity estimates by a methylation based (PAMES on WGBS data) versus a genomic based approach (CLONET on WES). Colors refer to the pathology classification. R is the Pearson's correlation coefficient. C) Beta values in plasma and tissue samples across portions of four genes of interest. ASXL3 and SPDEF were included in the NEPC classifier from Beltran and Prandi et al. CDH2 and INSM1 are associated with sites used in the NEPC feature score. Lines are fitted to

CRPC-Adeno (pink) and CRPC-NE (purple) samples medians of single CpG sites using loess function. Plasma CpG sites were filtered keeping only those presenting at least 2 measurements for each class. D) Comparison of average absolute z-score measured in tissue samples (Beltran et al. 2016) and plasma samples (this cohort) for the two target DMR sets reported in figure 6C. P-values are calculated with unpaired two-sided Wilcoxon-Mann-Whitney test. E) Box plots of the distribution of beta values in ctDNA samples for sites identified as differentially methylated in CRPC-NE vs CRPC-Adeno in tissue samples (hypo: AUC<0.2; hyper: AUC>0.8). P-value are calculated by Wilcoxon-Mann-Whitney test.



Supplementary Figure 9. Input DNA titration experiments for whole exome sequencing and deduplication analysis. A) Copy number profiles correlation for a set of cancer genes assessed from processed sequencing data from a series of titration experiment. The sample was selected based on tumor volume/tumor content. Data are shown from libraries built starting from 50ng, 20ng, 10ng, or 5ng, and processed with or without a filter to remove read duplicates (DR). B) Genome-wide view of copy number profiles of previous data is shown together with matched tumor tissue biopsy data. C) Percentiles of read duplicates distribution across plasma and germline samples and across different coverage intervals. D) Distributions of germline and plasma mean coverage across *ad-hoc* de-duplication strategies. E) Comparison of copy number profiles for a set of cancer genes obtained from sequencing data including read duplicates and upon deduplication using different strategies. See Online Methods. (SE = single end sequencing protocol, PE = paired end sequencing protocol, DR = inclusion of read duplicates).