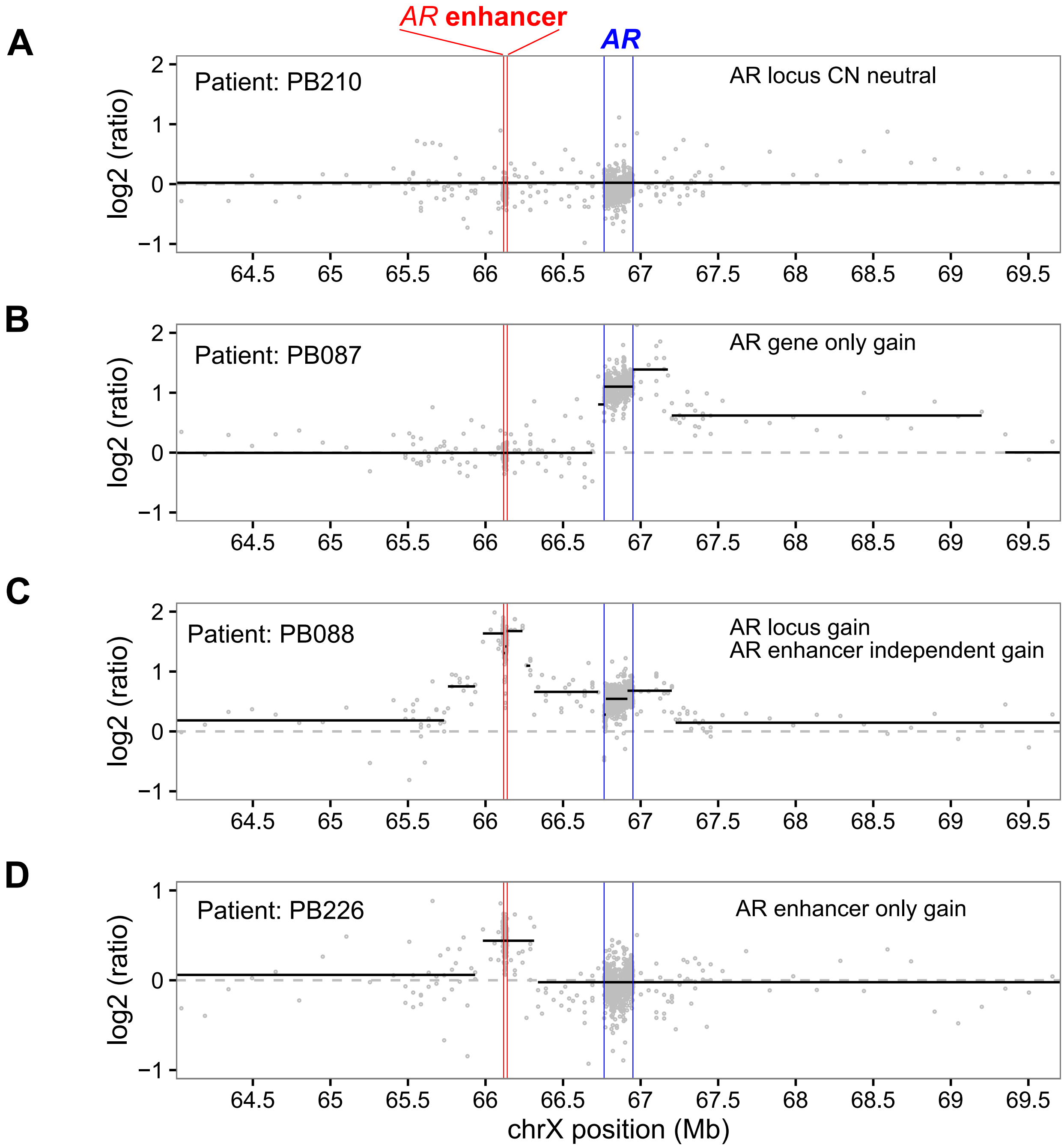


Fig A1. Examples of copy number determination in the *AR* enhancer and gene body from cell-free DNA. Each panel depicts the log2 copy number ratio of the *AR* locus and surrounding genomic space, from patient cell-free DNA normalized to matched plasma depleted whole blood targeted next-generation sequencing. Panel **A** indicates an example of a patient with no copy number alterations in the *AR* enhancer or gene body. Panel **B** depicts cell-free DNA from a patient with copy number gain in the *AR* gene body but not enhancer. Panel **C** shows a patient with cell-free DNA amplification of both the *AR* enhancer and gene body. Panel **D** represents a patient with cell-free DNA copy number gain in the *AR* enhancer but not gene body. *AR*, androgen receptor; log2, logarithm base 2; Mb, megabase.

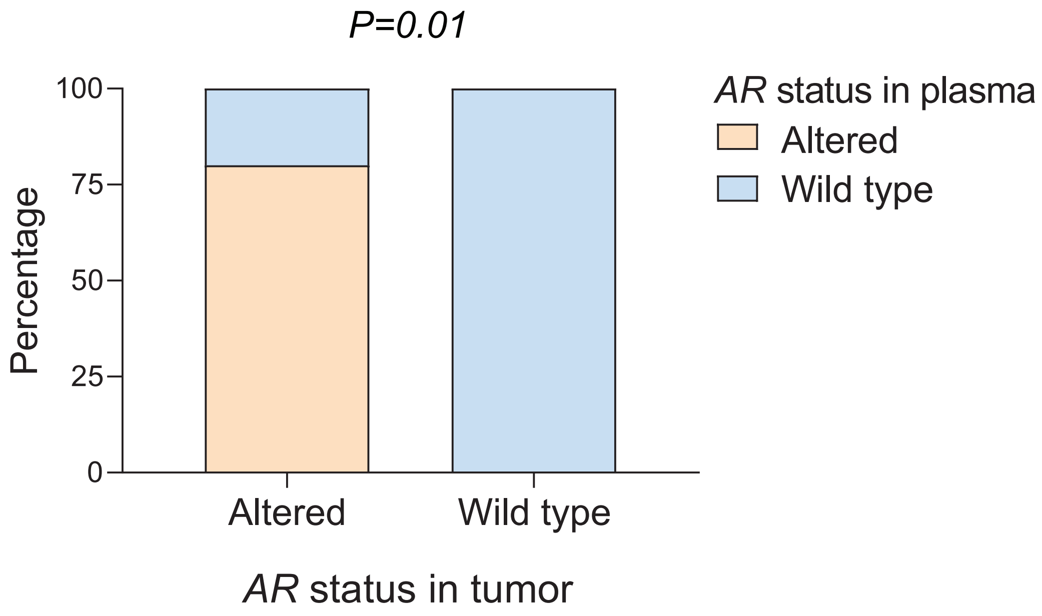


Fig A2. Comparison of *AR* gene body alterations detected by tumor and plasma cell-free DNA sequencing. Ten patients had samples available for this analysis. Targeted next-generation sequencing (NGS) was performed of tumor DNA (extracted from formalin-fixed paraffin-embedded tissue) and plasma cell-free DNA. *AR* genomic alterations were detected in 5 cases by tumor NGS with these same alterations present in 4 cases by plasma NGS. P value was calculated by the Fisher's exact test. *AR*, androgen receptor.

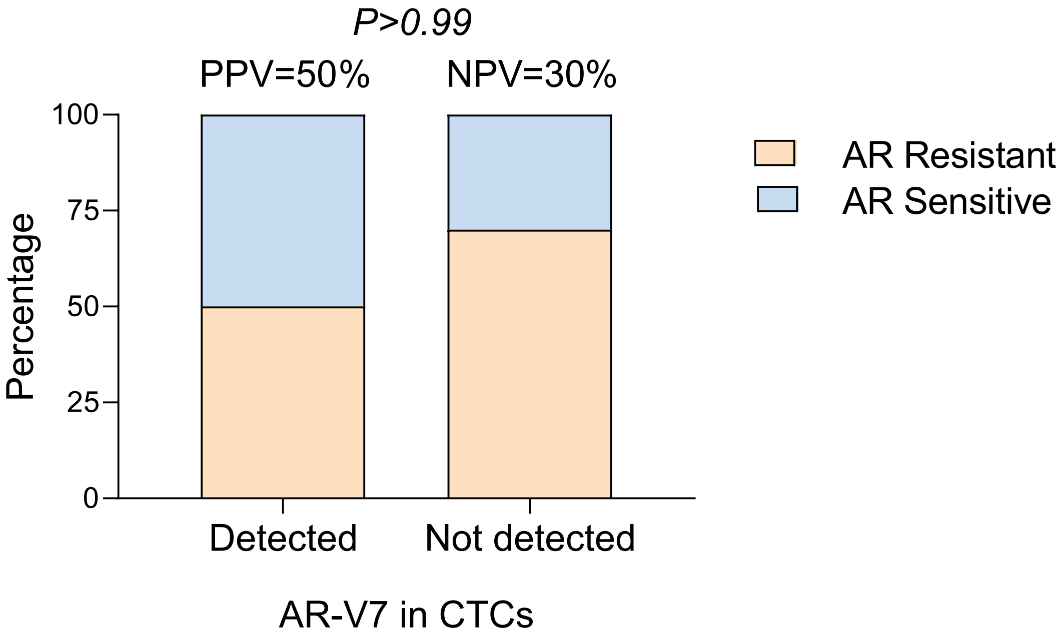
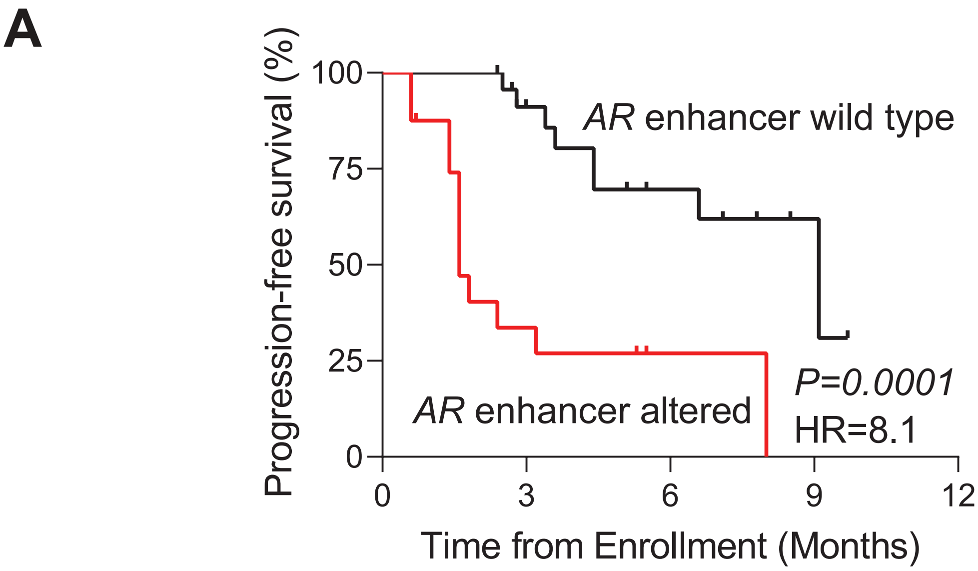
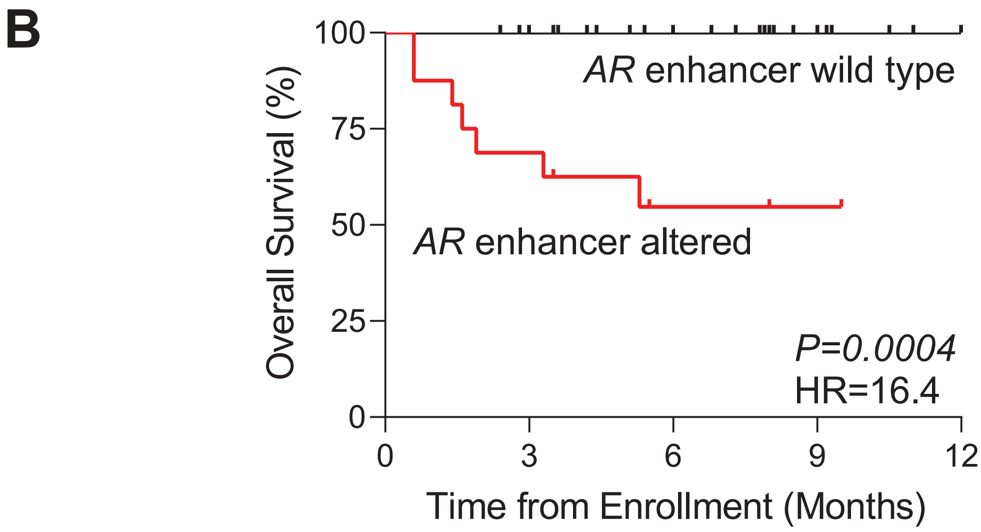


Fig A3. AR-V7 detection in circulating tumor cells and its association with resistance to AR-directed therapy in the present cohort. Proportion of patients with AR-V7 detected (N=2) or not (N=23) in circulating tumor cells, who developed resistance or not to AR-directed therapy. The positive and negative predictive values are displayed in each panel. P values were calculated using Fisher's exact test. PPV, positive predictive value; NPV, negative predictive value; *AR*, androgen receptor.



No. at Risk					
AR enhancer altered	16	5	1	0	0
AR enhancer wild type	24	18	9	2	0



No. at Risk					
AR enhancer altered	16	11	2	1	0
AR enhancer wild type	24	22	15	6	0

Fig A4. Progression-free and overall survival according to *AR* enhancer status in cell-free DNA. PFS is shown in panel **A** and OS is shown in panel **B**. For PFS, median was 1.6 months in patients with *AR* enhancer altered and 9.1 months in patients with wild type *AR* enhancer in cell-free DNA. For OS, median was not reached in either arm. Hazard ratio for PFS was 8.1 (95% CI, 2.8 to 23.6; *P=0.0001*) and 16.4 (95% CI, 3.5 to 77.2; *P=0.0004*) for OS. P values were calculated by the log-rank test. PFS, progression-free survival; OS, overall survival; *AR*, androgen receptor; HR, hazard ratio.

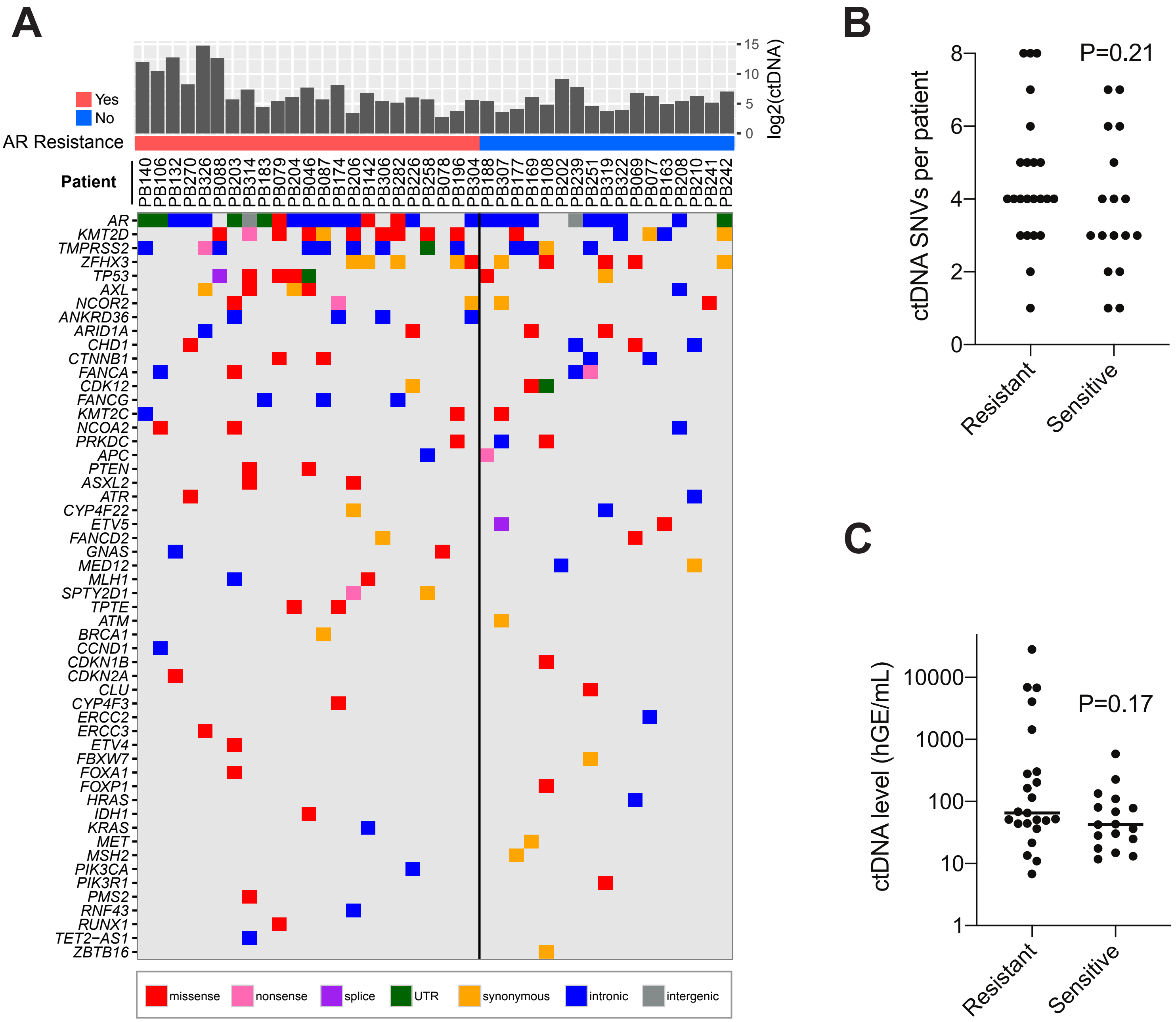


Fig A5. SNV-based analyses of mutational burden and ctDNA levels at baseline. **(A)** Heatmap of all somatic SNVs detected in each patient at time of enrollment. Genes are shown on the left and mutation types are indicated in the legend below. ctDNA levels are represented in the bar graph on top in log2 space. Resistance to AR-directed therapy is indicated below the bar graph as red (resistant) vs. blue (sensitive). **(B)** Comparison of the number of SNVs and **(C)** ctDNA levels in AR-resistant vs. sensitive patients. ctDNA levels are in haploid genome equivalents per mL; P-values were calculated by Student's t test.