Supplementary Figure legends

Supplementary Table 1: *SPOP* mutations identified in this CRPC cohort. Mutations, which have not been previously described in prostate cancer are highlighted in red.

Supplementary Table 2: Baseline prognostic factors from start of abiraterone for CHD1 IHC negative or positive CRPC patients.

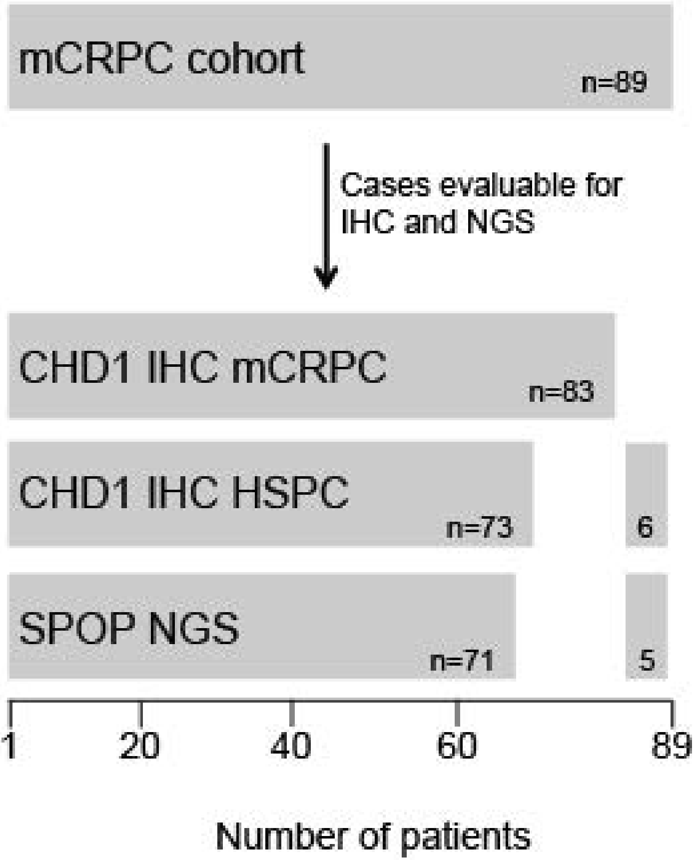
Supplementary Figure 1: A) Schematic summary of patient samples (HSPC, CRPC) analyzed by IHC and targeted NGS.

Supplementary Figure 2: A) Micrographs (20x) of tissue sections analyzed for CHD1 and PTEN expression. Both patients show co-occurring loss of CHD1 and PTEN. **B)** Histogram summarizing the distribution of mutated residues in the SPOP protein in three different CRPC cohorts. View focuses only on the affected amino acids spanning the MATH protein domain. RMH – Royal Marsden (this cohort), SU2C – SU2C/ PCF initiative for advanced prostate cancer, FRED – Fred Hutchinson Cancer Research Center cohort. **C)** CHD1 expression increases with tumor progression. H-scores of patient-matched HSPC and CRPC biopsies are shown (n=56, HSPC median: 65 (IQR: 30-88), CRPC median: 80 (IQR: 33-100), Wilcoxon signed-rank test p-value=0.010). **D, E)** Shannon indices based on 5p (F) and 5q (G) FISH probes alone. P-values were calculated using unpaired t-test.

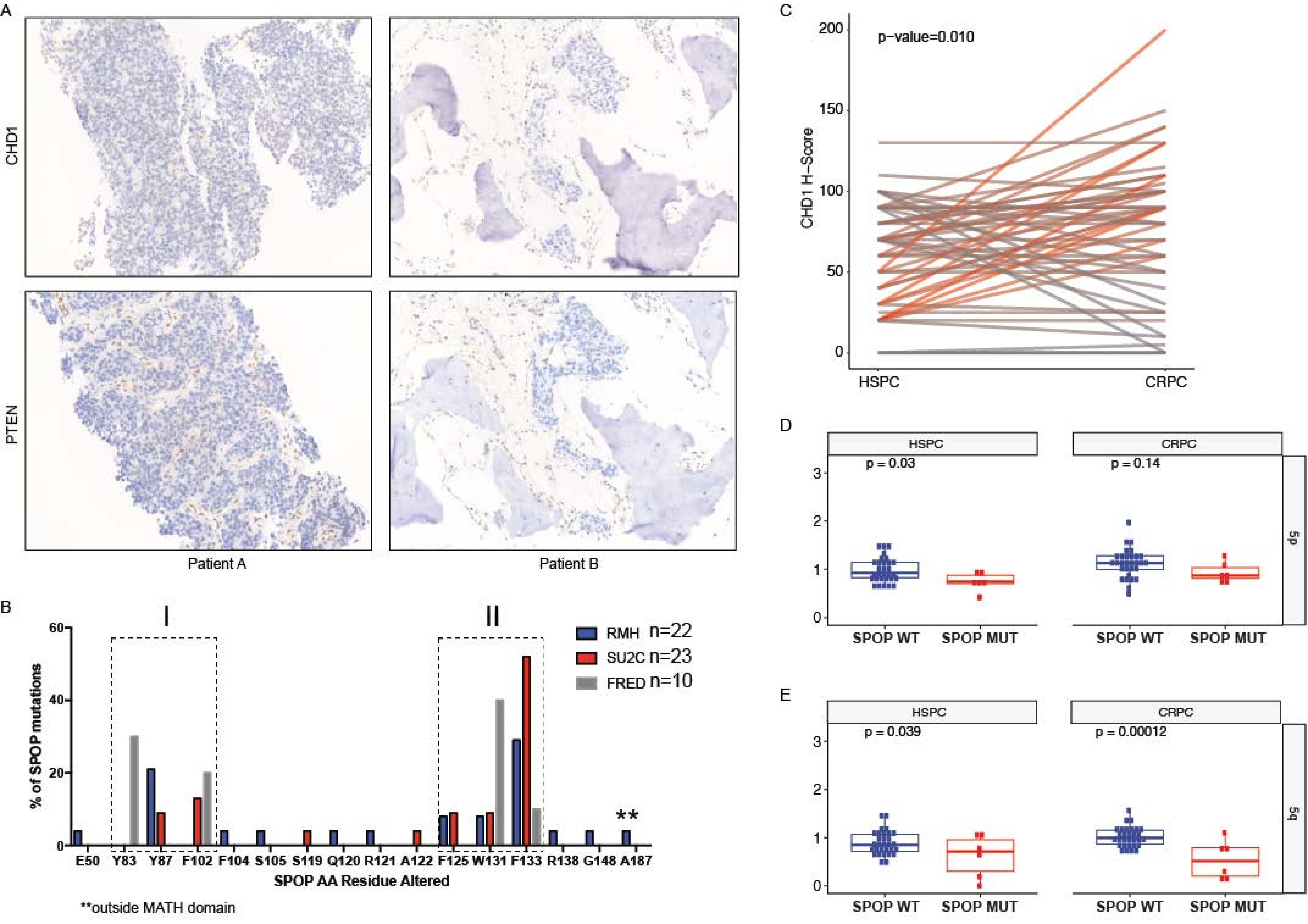
Supplementary Figure 3: Combined *SPOP* mutation and CHD1 loss by IHC status predict better and longer response to abiraterone (A, B). C) Waterfall plot showing increased PSA responses from start of abiraterone in $\text{CHD1}^{\text{LOSS}}$ plus SPOP^{MUT} versus CHD1^{WT} plus SPOP^{WT} tumors. Each bar represents PSA nadir from start of treatment for an individual patient. Dashed line indicates PSA fall by 50%. PSA nadir data were available for 37 patients with known SPOP status. P=0.023, 2-side Fisher's exact test.

Supplementary Figure 1

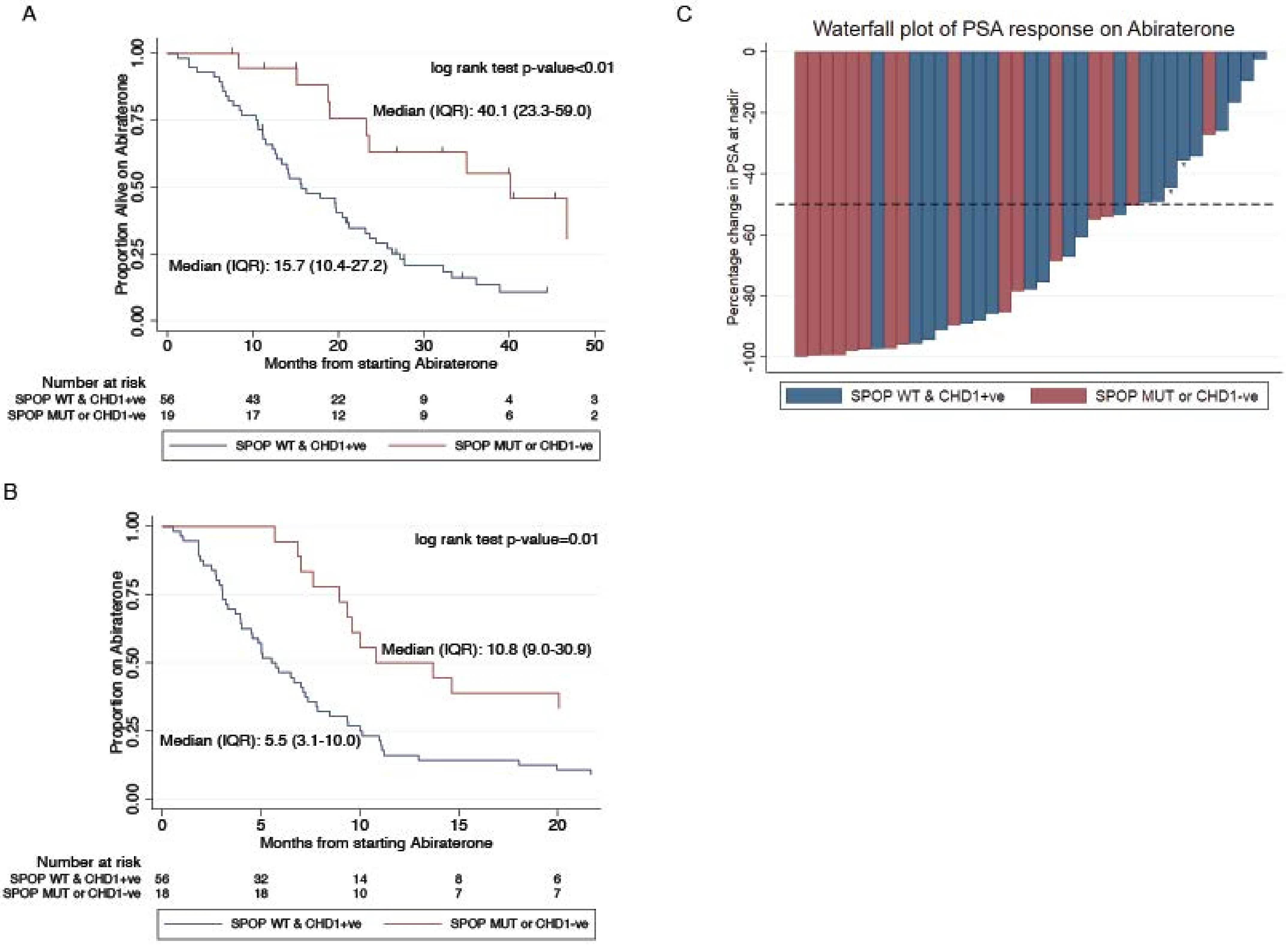
A



Supplementary Figure 2



Supplementary Figure 3



Supplementary Table 1: SPOP mutations identified in this cohort

Sample ID	**Protein Change**	**Codon Change**	**COSMIC ID**	**HSPC**	**CRPC**
PT1	p.A187T	c.559G>A	N/A	N/A	yes
PT2	p.F133S*, p.E50K**	c.398T>C*, c.148G>A**	COSM247573*,COSM980818**	yes*	yes**
PT3	p.F104S	c.311T>C	COSM3672491	N/A	yes
PT4	p.F125C	c.374T>G	N/A, SU2C (425)	N/A	yes
PT5	p.F125L	c.375T>A	COSM242643	N/A	yes
PT6	p.F133C	c.398T>G	COSM242645	yes	yes
PT7	p.F133L	c.399C>G	COSM95272	yes	N/A
PT8	p.F133L	c.399C>G	COSM95272	yes	N/A
PT9	p.F133L	c.399C>G	COSM95272	N/A	yes
PT10	p.F133V	c.397T>G	COSM219965	yes	yes
PT11	p.F133V	c.397T>G	COSM219965	N/A	yes
PT12	p.F133L	c.399C>G	COSM95272	N/A	yes
PT13	p.G148E	c.443G>A	N/A	no	yes
PT14	p.Q120R	c.359A>G	N/A	N/A	yes
PT15	p.R121P	c.362G>C	N/A	N/A	yes
PT16	p.S105F	c.314C>T	N/A	N/A	yes
PT17	p.W131C	c.393G>C	N/A, TCGA prostate	yes	yes
PT18	p.W131C	c.393G>C	N/A, TCGA prostate	N/A	yes
PT19	p.Y87C	c.260A>G	COSM248681	N/A	yes
PT20	p.Y87C	c.260A>G	COSM248681	yes	yes
PT21	p.Y87N	c.259T>A	COSM242640	yes	yes
PT22	p.Y87S	c.260A>C	COSM241746	N/A	yes

*	found only in HSPC
**	found only in CRPC

Supplementary Table 2: Baseline levels at start of abiraterone

	CHD1 negative in CRPC	**CHD1 positive in CRPC**	**P-value**
Baseline PSA, µg/l (median (IQR)	104 (33.25-719.8)	143 (67-357)	p=0.76
Baseline hemoglobin, g/dl (mean (±SD))	12.4 (±1.43)	11.9 (±1.59)	p=0.47
Baseline alkaline phosphatase, IU/l (median (IQR)	77.5 (58.5-127.8)	106 (68-227)	p=0.14
Baseline lactate dehydrognease, IU/l (median (IQR)	168 (151.5-260.5)	174 (155-248)	p=0.83
Baseline albumin, g/l (mean (±SD))	38 (±4.34)	35.86 (±4.27)	p=0.25
	SPOP MUT in CRPC	**SPOP WT in CRPC**	**P-value**
Baseline PSA, µg/l (median (IQR)	207 (26.5-543)	136.5 (69.25-374)	p=0.98
Baseline hemoglobin, g/dl (mean (±SD))	12 (±1.37)	11.8 (±1.47)	p=0.67
Baseline alkaline phosphatase, IU/l (median (IQR)	68 (53.5-155)	123.5 (70.5-244.3)	p=0.06
Baseline lactate dehydrognease, IU/l (median (IQR)	173 (143.5-234)	192 (154.3-296.3)	p=0.47
Baseline albumin, g/l (mean (SD))	37.67 (±4.77)	35.18 (±4.83)	p=0.17