

SUPPLEMENTAL INFORMATION

Table S1. Characteristics of patients in the study.

Patient #	Treatment in study	Haemolysis*	miR-1228 Ct	miR-141/1228 $2^{-\Delta Ct}$	miR-21/1228 $2^{-\Delta Ct}$	miR-223/1228 $2^{-\Delta Ct}$	tCRPC (months)	Hb (g/L)	PFS (months)	OS (months)	Previous therapy	Post-progression therapy
#1	Abiraterone Acetate	0.047	28.21	0.0038	2.2736	4.2428	49.7	140	3.73	37.07	0	Docetaxel > Cabazitaxel
#2	Enzalutamide	0.028	27.82	0.0057	3.6427	4.0139	19.2	131	39.40	42.17	0	Abiraterone
#3	Abiraterone Acetate	0.024	28.85	0.0196	2.1214	11.5115	32.3	148	17.23	32.77	0	Docetaxel
#4	Enzalutamide	0.051	29.25	0.0403	11.3924	15.5625	45.0	139	35.70	40.87	0	Docetaxel > Radium ²²³
#5	Enzalutamide	0.041	27.76	0.0121	3.1821	2.4538	48.9	135	15.17	40.63	0	Docetaxel > Cabazitaxel > Mitoxantrone
#6	Enzalutamide	0.065	27.17	0.0278	3.7711	4.8906	35.0	130	30.03	38.47	0	Radium ²²³
#7	Abiraterone Acetate	0.021	27.81	0.0277	6.5887	13.5479	33.1	135	39.90	39.90	Docetaxel	N/A
#8	Enzalutamide	0.014	29.09	0.0135	10.2319	5.4076	19.0	112	31.37	36.57	0	Ciclofosfamide
#9	Enzalutamide	0.028	27.15	0.0065	4.6589	5.1694	30.4	140	24.80	39.87	0	No therapy
#10	Enzalutamide	0.051	27.40	0.0139	5.7958	4.3469	111.3	122	6.80	6.80	0	No therapy
#11	Enzalutamide	0.125	27.89	0.0170	13.1775	12.1257	79.4	168	20.40	33.70	Docetaxel	No therapy
#12	Enzalutamide	0.056	23.53	0.2457	1.4743	0.8706	11.8	132	2.10	8.53	0	Radium ²²³
#13	Enzalutamide	0.045	27.68	0.2661	18.0009	12.2525	13.1	129	6.97	37.33	0	Docetaxel > Abiraterone > Cabazitaxel
#14	Enzalutamide	0.038	26.05	0.0711	7.8354	6.3864	56.4	135	38.50	38.50	0	No therapy
#15	Abiraterone Acetate	0.024	27.57	0.0375	9.2856	12.5969	4.2	135	30.33	37.10	0	Docetaxel > Cabazitaxel
#16	Abiraterone Acetate	0.053	25.87	0.0123	4.3772	10.9663	15.2	135	11.83	12.53	0	No therapy
#17	Enzalutamide	0.025	27.14	0.0235	2.9794	11.5915	78.0	133	36.70	36.70	0	N/A
#18	Enzalutamide	0	27.06	0.0374	11.7127	13.0412	47.8	100	4.13	4.13	0	No therapy

#19	Abiraterone Acetate	0.055	24.44	0.2956	2.0023	0.7178	9.1	113	5.80	5.93	0	No therapy
#20	Enzalutamide	0.005	24.64	0.0252	0.9255	1.0163	8.0	110	2.10	3.43	0	No therapy
#21	Enzalutamide	0.068	27.29	0.0171	6.4086	10.7406	46.3	131	12.60	21.20	0	Radium ²²³
#22	Abiraterone Acetate	0.058	26.74	0.0224	4.5473	5.5983	60.8	114	19.57	35.93	0	Docetaxel > Enzalutamide > Cabazitaxel
#23	Enzalutamide	0.002	23.61	0.2293	1.8088	0.3143	38.1	119	12.17	17.53	0	No therapy
#24	Abiraterone Acetate	0.09	27.27	0.0108	6.2767	10.0561	87.2	134	29.40	33.60	0	Docetaxel > Cabazitaxel
#25	Abiraterone Acetate	0.1	25.91	0.2003	5.3147	6.7039	39.8	133	28.67	33.57	Docetaxel	Cabazitaxel
#26	Enzalutamide	0.076	26.13	0.0077	8.9074	20.3930	66.6	131	17.23	32.43	Docetaxel	Cabazitaxel
#27	Enzalutamide	0.083	25.23	0.0046	3.7581	6.5432	28.9	139	31.80	32.50	0	Docetaxel
#28	Enzalutamide	0.051	26.33	0.0052	4.7404	11.4320	20.7	142	32.40	32.40	0	best supportive care
#29	Enzalutamide	0.012	26.35	0.0409	2.6851	4.1125	83.0	118	9.60	20.70	0	best supportive care
#30	Abiraterone Acetate	0.076	27.49	0.0409	9.3827	10.4831	46.6	128	30.50	30.50	Docetaxel	N/A
#31	Enzalutamide	0.024	26.83	0.3078	5.7557	4.0558	6.6	127	8.80	20.33	0	Docetaxel

*Haemolysis was measured as free Hb (g/L) corrected for lipoprotein content as described in the Materials and Methods.

Table S2. Association of patients' clinical and biological characteristics with PFS.

Variable		Univariate analysis						Multivariate analysis		
		E/N	Median (95% CI)	Logrank p-value ^{BH}	HR	95% CI	P-value ^{BH}	HR	95% CI	p-value
PFS		26/31	19.3 (11.7-29.6)							
Treatment	Abiraterone	8/10	23.8 (3.7-29.9)	0.8412	1					
	Enzalutamide	18/21	17.0 (8.7-30.9)		1.09	0.47-2.53	0.8405			
PSA (ng/mL)	≤7.45	6/8	32.5 (4.1-)	0.2618	1					
	>7.45	20/23	14.9 (8.7-28.3)		1.83	0.73-4.60	0.2650			
tCRPC (months)	≤15.2	7/7	6.9 (2.1-11.7)	0.0039	4.09	1.62-10.33	0.0068	4.8	1.65-14	0.004
	>15.2	19/24	26.3 (14.9-30.9)		1					
N/L	≤1.48	8/10	29.4 (12.0-31.3)	0.2618	1					
	>1.48	18/21	12.4 (6.7-28.3)		1.71	0.74-3.94	0.2650			
Hb (g/L)	≤127	9/9	8.7 (2.1-19.3)	0.0039	3.67	1.54-8.75	0.0068	2.3	0.70-7.2	0.171
	>127	17/22	28.6 (14.9-35.2)		1					
ECOG PS	0	7/10	28.6 (8.7-)	0.2618	1					
	1-2	19/21	17.0 (6.7-29.6)		1.74	0.73-4.16	0.2650			
Gleason score	≤7	5/7	24.4 (3.7-)	0.8221	1					
	>7	19/21	19.3 (9.5-29.9)		1.18	0.43-3.22	0.8255			
miR-21/1228	≤2.69	7/7	5.7 (2.1-)	0.0002	7.38	2.56-21.25	0.0021	4.8	1.29-17.8	0.019
	>2.69	19/24	28.6 (19.3-35.2)		1					
miR-141/1228	≤0.20	21/26	26.3 (14.9-30.9)	0.0010	1					
	>0.20	5/5	6.9 (2.1-)		7.43	2.18-25.37	0.0068	1.2	0.27-5.6	0.79
miR-223/1228	≤4.35	10/10	7.7 (2.1-12.0)	0.0039	3.52	1.52-8.13	0.0068	2.0	0.62-6.3	0.246
	>4.35	16/21	29.0 (17.0;31.3)		1					

Abbreviations: PSA, prostate-specific antigen; tCRPC, time to development of castration-resistance; N, neutrophils; Ly, lymphocytes; N/L, neutrophil-lymphocyte ratio; Hb, hemoglobin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BH, Benjamini-Hochberg correction.

Table S3. Association of patients' clinical and biological characteristics with OS.

		Univariate analysis						Multivariate analysis		
		E/N	Median (95% CI)	Logrank p-value ^{BH}	HR	95% CI	p-value ^{BH}	H R	95% CI	p-value
OS		13/31	-							
Treatment	Abiraterone	3/10	-	0.4376	1					
	Enzalutamide	10/21	36.0 (20.0-)		1.66	0.46-6.05	0.4424			
PSA (ng/mL)	≤7.45	1/8	-	0.1691	1					
	>7.45	12/23	36.0 (20.0-)		4.45	0.58-34.27	0.2171			
tCRPC (months)	≤15.2	5/7	12.4 (3.4-)	0.0405	3.5	1.14-10.94	0.0594	7.6 1	1.43-40.5	0.017
	>15.2	8/24	-		1					
N/L	≤1.48	3/10	-	0.2949	1					
	>1.48	10/21	-		2.05	0.56-7.47	0.3067			
Hb (g/L)	≤127	8/9	17.3 (3.4-)	0.0003	8.01	2.55-25.16	0.0036	8.9 7	2.24-35.8	0.002
	>127	5/22	-		1					
ECOG PS	0	2/10	-	0.1691	1					
	1-2	11/21	33.2 (12.4-)		3.12	0.69-14.11	0.2171			
Gleason score	≤7	1/7	-	0.1808	1					
	>7	11/21	36.0 (17.3-)		4.10	0.53-31.91	0.2225			
miR-21/1228	≤2.69	6/7	17.3 (36.0-)	0.0067	5.16	1.70-15.70	0.0191	5.7 7	1.01-33.1	0.049
	>2.69	7/24	-		1					
miR-141/1228	≤0.20	9/26	-	0.0405	1					
	>0.20	4/5	17.3 (5.8-)		3.82	1.14-12.79	0.0594	1.8 7	0.32-10.8	0.484
miR-223/1228	≤4.35	7/10	18.7 (3.4-)	0.0357	3.82	1.27-11.52	0.0577	0.8 4	0.12-5.9	0.862
	>4.35	6/21	-		1					

Abbreviations: PSA, prostate-specific antigen; tCRPC, time to development of castration-resistance; N, neutrophils; Ly, lymphocytes; N/L, neutrophil-lymphocyte ratio; Hb, hemoglobin; ECOG PS, Eastern Cooperative Oncology Group Performance Status. BH: Benjamini-Hochberg correction.

Table S4. Correlations among patients' clinical and biological characteristics.

Row	Column	Cor (Spearman)	<i>p</i> -value ^{BH}
PSA	tCRPC	-0.14	0.8346
PSA	N/L	-0.02	0.9074
tCRPC	N/L	-0.09	0.8964
PSA	Hb	0.07	0.8964
tCRPC	Hb	0.07	0.8964
N/L	Hb	-0.07	0.8964
PSA	miR-21/1228	-0.26	0.5586
tCRPC	miR-21/1228	0.17	0.7720
N/L	miR-21/1228	-0.26	0.5586
Hb	miR-21/1228	0.06	0.7558
PSA	miR-141/1228	0.21	0.2567
tCRPC	miR-141/1228	-0.24	0.5655
N/L	miR-141/1228	-0.02	0.9074
Hb	miR-141/1228	-0.45	0.1218
miR-21/1228	miR-141/1228	0.05	0.8964
PSA	miR-223/1228	-0.29	0.5586
tCRPC	miR-223/1228	0.19	0.7243
N/L	miR-223/1228	-0.04	0.8964
Hb	miR-223/1228	0.37	0.2821
miR-21/1228	miR-223/1228	0.71	0
miR-141/1228	miR-223/1228	-0.13	0.8774

Abbreviations: PSA, prostate-specific antigen; tCRPC, time to development of castration-resistance; N, neutrophils; Ly, lymphocytes; N/L, neutrophil-lymphocyte ratio; Hb, hemoglobin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BH, Benjamini-Hochberg correction.

Figure S1. Kaplan-Maier curves showing clinical and biological characteristics identified as significant in univariate analysis for PFS (left panels) and OS (right panels).



