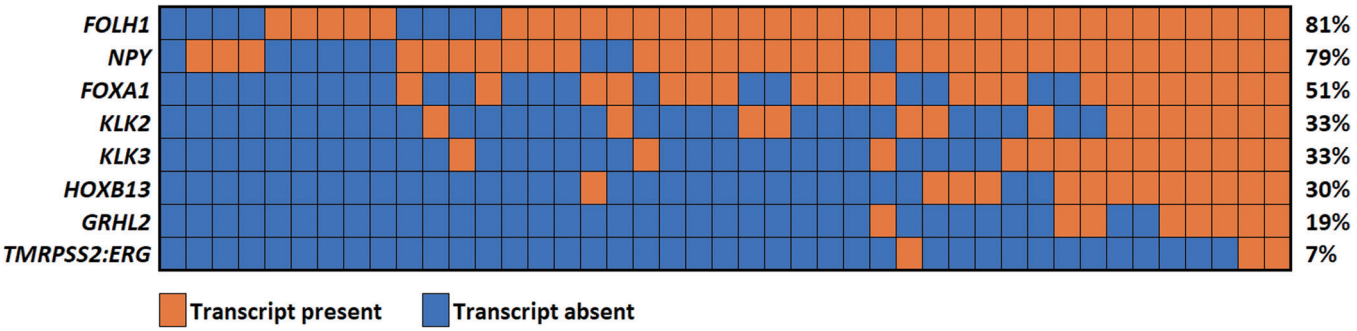

Figure S1 Distribution of circulating gene panel transcripts in the mHSPC cohort. Each column represents an individual patient sample. Percentage of patient samples positive for each transcript is shown on the right.

Table S1 Seven-month undetectable PSA rates according to presence of gene panel transcripts

	Undetectable PSA (%)[#]	P[†]
FOLH1 (+ *vs.* –)	18/32 (56) *vs.* 4/7 (57)	1.0
FOXA1 (+ *vs.* –)	10/19 (53) *vs.* 12/20 (60)	0.96
GRHL2 (+ *vs.* –)	2/8 (25) *vs.* 20/31 (65)	0.24
HOXB13 (+ *vs.* –)	4/12 (33) *vs.* 18/27 (66)	0.24
KLK2 (+ *vs.* –)	6/12 (50) *vs.* 16/27 (59)	0.96
KLK3 (+ *vs.* –)	5/13 (38) *vs.* 17/26 (65)	0.27
NPY (+ *vs.* –)	17/31 (55) *vs.* 5/8 (63)	1.0
TMPRSS2 (+ *vs.* –)	2/3 (66) *vs.* 20/36 (56)	1.0

[#]Based on 39 patients with available seven-month PSA data. [†]Calculated using Chi-square statistics (or Fisher's exact test if the expected frequency of the variable was less than 5) and adjusted for multiple testing using the standard Benjamini-Hochberg correction.

Table S2 Univariable Cox proportional hazard analysis of baseline clinicopathological factors associated with time to castration resistance

	HR	95% CI	P
Gleason score (≥8 *vs.* ≤7)	0.53	0.087–3.2	0.5
ECOG PS (2 *vs.* 0-1)	4.9	0.95–25	0.057
Visceral disease (yes *vs.* no)	2.3	0.47–11	0.3
Disease volume (high *vs.* low)	4.6	1.1–19	0.03
Treatment intensification# (yes *vs.* no)	0.62	0.16–2.3	0.47
Haemoglobin (< LLN *vs.* ≥ LLN)	0.94	0.90–0.98	0.03

All P values <0.05 are highlighted in bold. [#]Treatment intensification includes either docetaxel or AR pathway inhibitors as upfront therapy with ADT.

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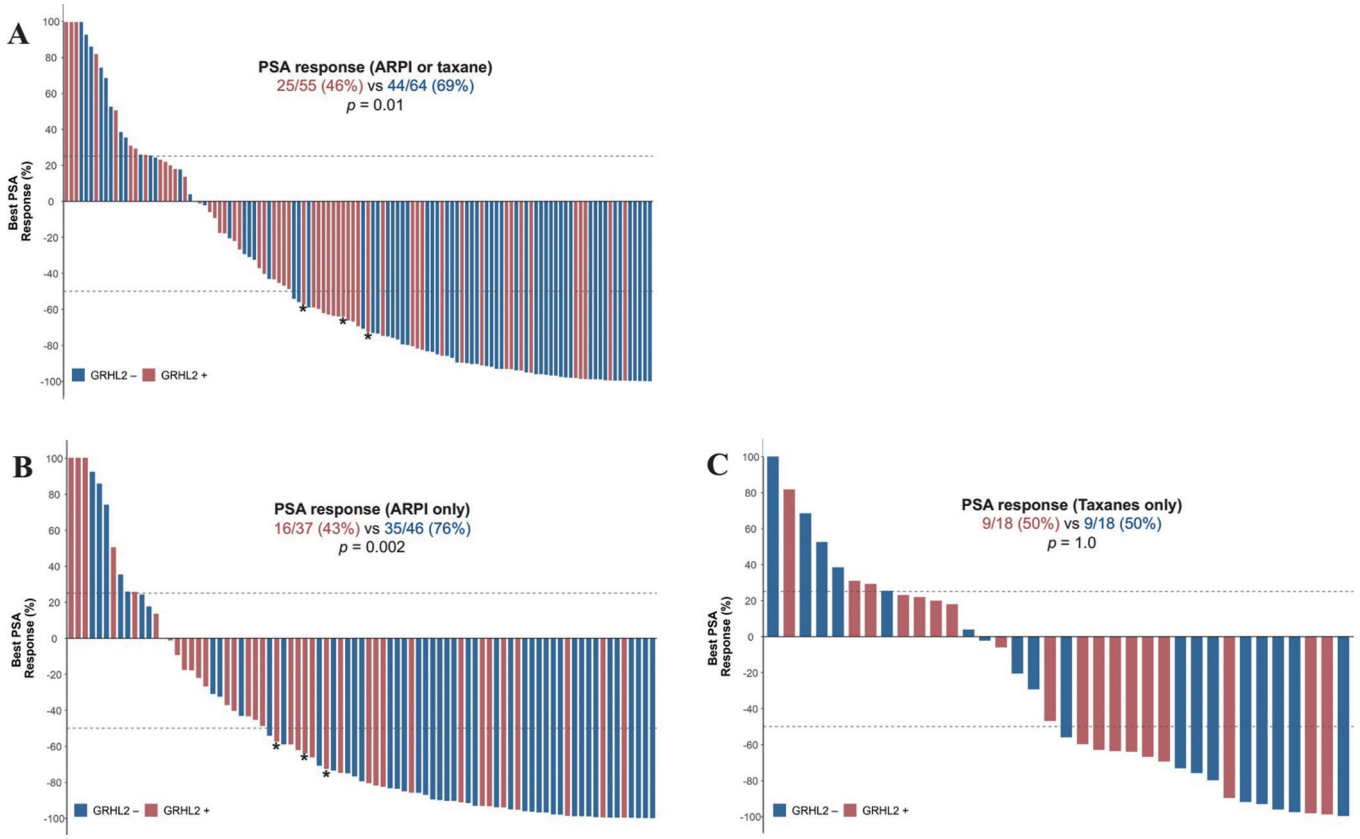

Figure S2 Waterfall plots of best PSA response and rates of confirmed PSA_{50} response according to *GRHL2* status and treatment received. Red bars represent *GRHL2*-positive patients and blue bars represent *GRHL2*-negative patients. Asterisk indicates non-confirmed PSA_{50} response. ARPI, androgen receptor pathway inhibitor (abiraterone acetate or enzalutamide).

Table S3 Univariable Cox proportional hazard analysis of clinical outcomes in the mCRPC cohort based on baseline clinicopathological factors

Variable	Progression-free survival			Overall survival		
	HR	95% CI	P	HR	95% CI	P
Gleason score (≥ 8 *vs.* ≤ 7)	1.3	0.72–2.2	0.4	1.1	0.54–2.1	0.9
Prior chemotherapy (yes *vs.* no)	1.4	0.88–2.2	0.2	1.6	0.97–2.7	0.07
Prior ARPI (yes *vs.* no)	2.8	1.6–4.6	<0.001	2.7	1.6–4.7	<0.001
ECOG PS (2 *vs.* 0-1)	1.5	0.66–3.2	0.4	2.5	1.1–5.5	0.03
Visceral disease (yes *vs.* no)	1.4	0.63–3.0	0.4	2.2	0.97–4.8	0.058
Haemoglobin (< LLN *vs.* ≥ LLN)	2.5	1.5–4.1	<0.001	3.0	1.6–5.4	<0.001

All P values <0.05 are highlighted in bold. ARPI, androgen receptor axis pathway inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ALP, alkaline phosphatase; NLR, neutrophil-lymphocyte ratio.

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