Supplemental Table 1 Characteristics of study population (*n* = 50).

Parameter	Total study population	Subgroup without influencing factors	Subgroup with influencing factors	*P* Value
Number (n)	50 (100%)	29 (58%)	21 (42%)	-
Age (years)	71.9 ±7.9 (52-86)	70.2 ± 8.4 (52 to 84)	74.4 ± 6.5 (63 to 86)	0.08
Gleason grade (median (range))	8 (6 to 10)	8 (6 to 10)	8 (7 to 9)	0.60
Blood-based parameters*				
Pre-treatment PSA (µg/l)	423.8 ± 674.7 (3.8 to 3205)	498.4 ± 809.8 (3.8 to 3205)	320.8 ± 422.1 (5.3 to 1394)	0.67
ProGRP (ng/ml)	75 ± 71 (29 to 305)	65 ± 37 (29 to 210)	89 ± 64 (30 to 305)	0.08
NSE (µg/l)	31 ± 24 (9 to 152)	33 ± 29 (13 to 152)	28 ± 14 (9 to 67)	0.89
CgA (µg/l)	191 ± 212 (33 to 1241)	119 ± 118 (33 to 687)	290 ± 271 (46 to 1241)	**0.0001**
Hemoglobin (g/dL)	11.5 ± 1.6 (7.3 to 13.9)	11.7 ± 1.7 (8.6 to 13.9)	11.3 ± 1.6 (7.3 to 13.8)	0.29
Erythrocyte count (10^6/µL)	3.9 ± 0.6 (2.6 to 4.8)	4.0 ± 0.6 (2.7 to 4.8)	3.8 ± 0.5 (2.6 to 4.7)	0.18
Leukocyte count (10^3/µL)	6.9 ± 2.1 (3.2 to 13.6)	6.7 ± 2.1 (3.5 to 13.6)	7.2 ± 2.0 (3.2 to 11.6)	0.11
Platelets (10^3/µL)	238 ± 82 (107 to 480)	243 ± 74 (131 to 378)	231 ± 93 (107 to 480)	0.37
Alkaline phosphatase (U/L)	230 ± 201 (43 to 950)	235 ± 210 (43 to 950)	224 ± 192 (44 to 636)	0.71
Lactate dehydrogenase (µmol/L)	383 ± 283 (83 to 1694)	378 ± 323 (83 to 1694)	383 ± 220 (195 to 954)	0.25
Site of metastases (no. of patients)				
Bone	45 (90%)	27 (93%)	18 (86%)	0.64
Lymph nodes	40 (80%)	23 (79%)	17 (81%)	1.0
Liver	14 (28%)	9 (31%)	5 (24%)	0.75
Lung	5 (10%)	4 (14%)	1 (5%)	0.38
Previous therapy (no. of patients)				
Androgen-deprivation therapy	50 (100%)	29 (100%)	21 (100%)	1.0
Arbiraterone acetate	35 (70%)	21 (72%)	14 (67%)	0.76
Enzalutamide	32 (64%)	16 (55%)	16 (76%)	0.15
Chemotherapy				
Docetaxel (1st line)	44 (88%)	26 (90%)	18 (86%)	0.69
Cabazitaxel (2nd line)	13 (26%)	9 (31%)	4 (19%)	0.52
Carboplatin (2nd/3rd line)	3 (6%)	2 (7%)	1 (5%)	1.0
External radiation therapy	41 (82%)	24 (83%)	17 (81%)	1.0

Supplemental Table 2 Univariate predictors of treatment response after 2 cycles of ^{177}Lu-PSMA-617

Parameter	Total study population (*n* = 50)			Subgroup without non-oncologic marker influencing factors (*n* = 29)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Blood-based parameters						
Hemoglobin	1.415	0.9682 to 2.191	0.0904	1.277	0.774 to 2.271	0.3574
Erythrocyte count	1.432	0.5034 to 4.423	0.5097	1.069	0.2515 to 4.988	0.9279
Thrombocyte count	1.004	0.9972 to 1.012	0.2449	1.003	0.925 to 1.015	0.5420
Leucocyte count	1.054	0.7915 to 1.405	0.7146	1.106	0.7485 to 1.636	0.5916
Lactate dehydrogenase (LDH)	0.9989	0.9959 to 1.001	0.4077	0.9966	0.9886 to 1.001	0.2484
Alkaline phosphatase (ALP)	0.9990	0.9956 to 1.002	0.5229	0.9995	0.9948 to 1.003	0.7934
Alanine transaminase (ALT)	0.9649	0.9035 to 1.001	0.1444	0.9245	0.7910 to 1.008	0.2611
Aspartate transaminase (AST)	0.9886	0.9666 to 1.006	0.2322	0.9474	0.8502 to 0.9962	0.1706
Gamma-glutamyltransferase (GGT)	0.9961	0.9842 to 1.000	0.2896	0.9891	0.9593 to 1.000	0.3635
Prostate-specific antigen (PSA)	0.9993	0.9977 to 1.000	0.2687	0.9995	0.99676 to 1.001	0.4872
Progastrin-releasing peptide (ProGRP)	1.010	0.9983 to 1.026	0.1269	1.009	0.9871 to 1.034	0.4125
Neuron-specific enolase (NSE)	1.004	0.7034 to 1.359	0.9794	0.9637	0.8763 to 1.008	0.3092
Chromogranin-A (CgA)	1.001	0.9979 to 1.004	0.6010	1.000	0.9905 to 1.007	0.9972
Imaging parameters						
Lymph node metastases	0.5385	0.1285 to 2.238	0.3860	0.3529	0.05138 to 2.353	0.2702
Osseous metastases	0.1250	0.006099 to 0.9356	0.0735	0.4211	0.01533 to 11.52	0.5578
Hepatic metastases	0.3636	0.07269 to 1.411	0.1690	0.6190	0.07652 to 3.589	0.6105
Intense PSMA-ligand uptake	11.77	2.743 to 82.81	**0.0030**	6.500	1.194 to 52.38	**0.0439**

CI – confidence interval; OR – Odds ratio

Supplemental Table 3 Univariate predictors of early progression after 2 cycles of ^{177}Lu-PSMA-617

Parameter	Total study population (*n*=50)			Subgroup without non-oncologic NE marker influencing factors (*n*=29)		
	OR	95% CI	P value	OR	95% CI	P value
Blood-based parameters						
Hemoglobin	0.7111	0.4755 to 1.024	0.0765	0.8595	0.5342 to 1.354	0.5145
Erythrocyte count	0.7864	0.2735 to 2.248	0.6490	1.379	0.3557 to 5.832	0.6441
Thrombocyte count	0.9946	0.9860 to 1.002	0.1823	0.9887	0.9753 to 0.9997	0.0633
Leucocyte count	1.080	0.8127 to 1.445	0.5919	0.9647	0.6536 to 1.385	0.8433
Lactate dehydrogenase (LDH)	1.002	0.9995 to 1.004	0.1594	1.002	0.9991 to 1.006	0.2624
Alkaline phosphatase (ALP)	1.001	0.9984 to 1.004	0.3892	1.001	0.9972 to 1.005	0.6508
Alanine transaminase (ALT)	1.011	0.9844 to 1.041	0.4063	1.014	0.9754 to 1.068	0.4862
Aspartate transaminase (AST)	1.010	0.9942 to 1.027	0.2170	1.024	0.9988 to 1.062	0.1062
Gamma-glutamyltransferase (GGT)	0.999	0.9979 to 1.001	0.8871	0.9997	0.9970 to 1.001	0.7294
Prostate-specific antigen (PSA)	1.001	0.998 to 1.002	0.1678	1.001	0.9997 to 1.002	0.2697
Progastrin-releasing peptide (ProGRP)	1.001	0.9888 to 1.013	0.8601	1.004	0.9832 to 1.028	0.6884
Neuron-specific enolase (NSE)	1.007	0.9816 to 1.035	0.5772	1.002	0.9733 to 1.031	0.8860
Chromogranin-A (CgA)	1.001	0.9977 to 1.003	0.6768	1.003	0.9966 to 1.016	0.4111
Clinical parameters						
Lymph node metastases	0.5385	0.1285 to 2.238	0.3860	0.7692	0.1190 to 4.949	0.7751
Osseous metastases	_	_	0.1424*	_	_	0.4877*
Hepatic metastases	1.269	0.3487 to 4.493	0.7110	0.4500	0.07621 to 2.252	0.3437
Intense PSMA-ligand uptake	0.2029	0.05604 to 0.6721	**0.0111**	0.1364	0.02206 to 0.6610	**0.0192**

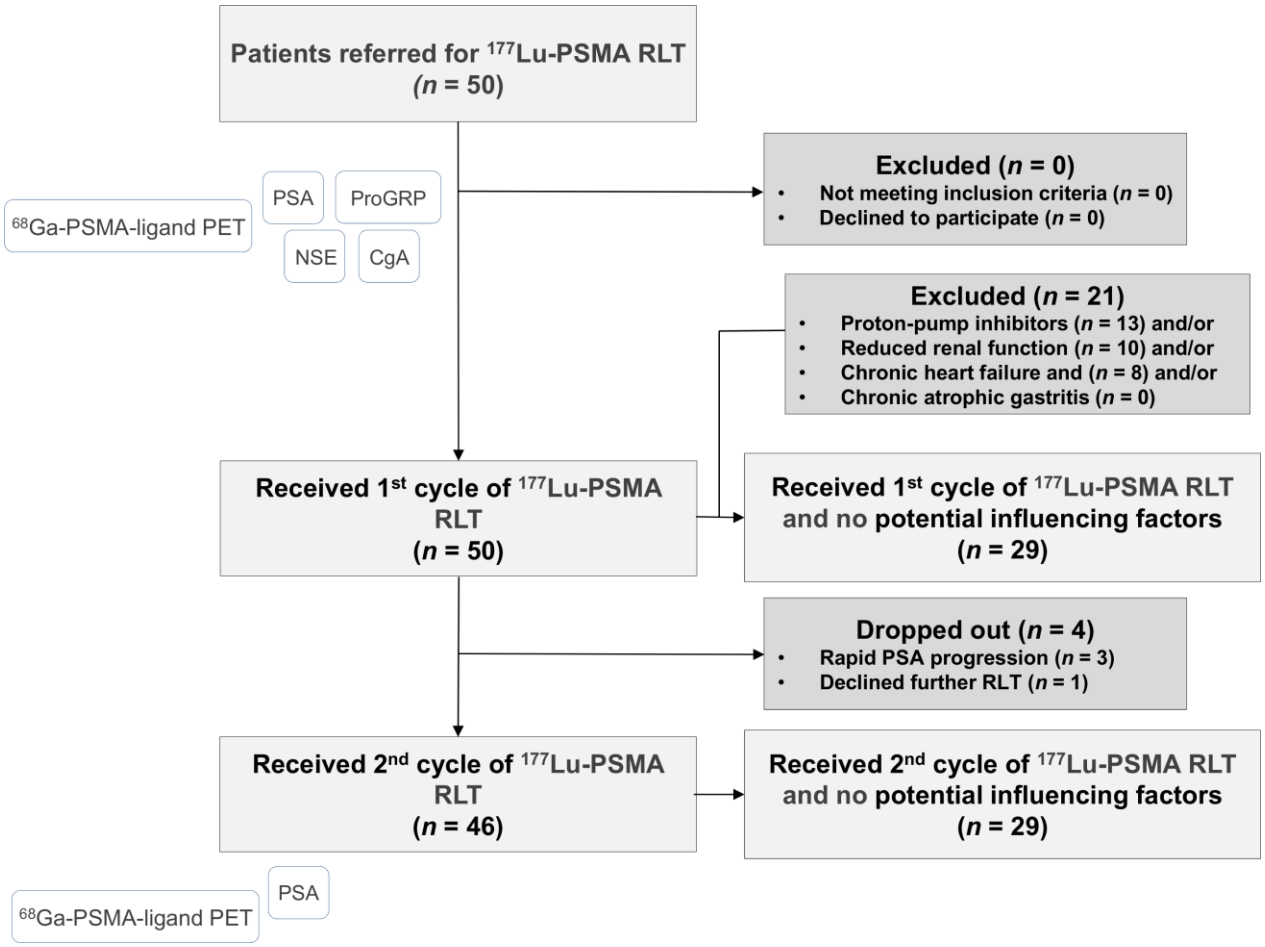
**P values were calculated using Fisher`s exact test because a logistic regression could not be fitted for patients with osseous metastases (all patients who progressed had bone metastases). CI – confidence interval; OR – Odds ratio*

Supplemental Table 4 Neuroendocrine marker expression, neuroendocrine serum marker levels, and outcome in patients with available histological specimens (*n* = 5)

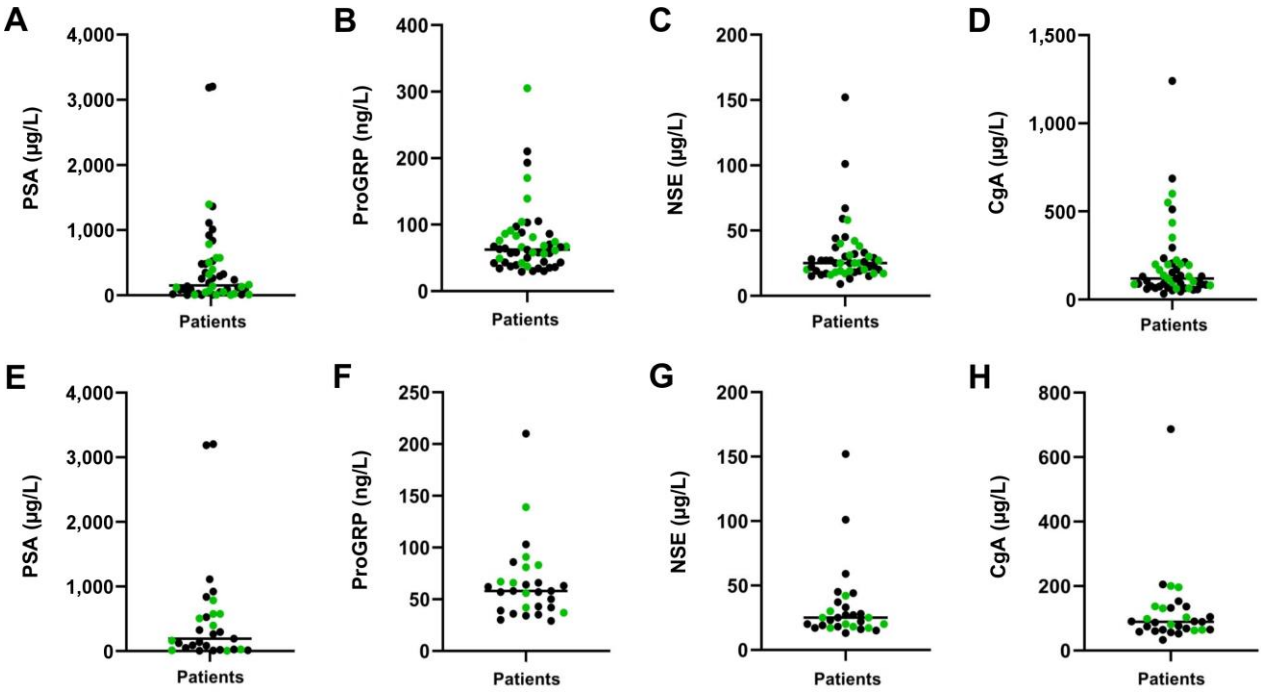
Specimen	Hormone-responsiveness	Serum markers			Immunohistochemistry		PSMA-ligand uptake	Outcome after 2 cycles of ^{177} PSMA	
		ProGRP (ng/l)	NSE (µg/l)	CgA (µg/l)	NSE	CgA		PSA response	Early progres
Prostate biopsy	castration-sensitive	64	13	136	-	-	intense	n	n
Prostatectomy	castration-sensitive	35	16	74	+	-	low	n	n
TURP specimen	castration-sensitive	81	25	196	+ to ++	-	intense	y	n
Peritoneal metastasis	castration-resistant	68	40	168	+	-	intense	y	n
Bone metastasis	castration-resistant	170	31	435	-	-	intense	y	n

CgA - chromogranin-A; NSE - neuron-specific enolase; ProGRP - progastrin-releasing peptide; PSA – prostate-specific antigen; PSMA – prostate-specific membrane antigen; TURP - transurethral resection of *the* prostate

Supplemental Figures



Supplemental Figure 1 *Flowchart of study cohort included in the analysis (n = 50).* 50 consecutive patients with mCRPC commencing ^{177}Lu-PSMA-617 radioligand therapy were included in the analysis, and had undergone pretreatment ^{68}Ga-PSMA ligand PET, assessment of PSA levels and screening for neuroendocrine differentiation. Outcome was evaluated after 2 cycles of ^{177}Lu-PSMA-617, based on PSA change and restaging PET. Analyses were performed for both the total study population and a subgroup of patients without non-oncologic factors potentially influencing serum levels of neuroendocrine markers (*n* = 29).



Supplemental Figure 2 *Pre-treatment serum levels of secreted neuroendocrine markers in mCRPC patients commencing ^{177}Lu-PSMA-617 radioligand therapy.* Serum PSA for comparison (**A**). Markers were elevated in the majority of patients, and showed marked interindividual variability (ProGRP, range 29-305 ng/l (**B**); NSE, range 9-152 µg/l (**C**); and CgA, range 33-1241 µg/l (**D**)). *Upper limit of normal is 40 ng/l for ProGRP, 16 µg/l for NSE, and 76 µg/l for CgA.* In the subgroup of patients without potential non-oncologic influencing factors (*n* = 29), PSA and markers demonstrated a similar distribution with high interindividual variability (**E-H**). *Responders are marked in green.*