

**Supplementary Table S1. Relative tumor volumes,  $^{177}\text{Lu-}/^{225}\text{Ac-PSMA617}$  uptake and 53BP1 IRS.** Relative tumor volumes (rTV) represent the fold change of the tumor volume on day 14 (studies 1, 2), day 88 (study 3), or day 24 (study 4) compared to the respective pre-treatment volumes. Radioligand uptake and DNA damage was assessed in tumors (n=3/group) resected two days after RLT. Mean $\pm$ SD and range (in parentheses) are shown.

study	group	rTV	uptake [%IA/g]	53BP1 [IRS]
<b>1. PSMA levels/cell in the RM1 model; <math>^{177}\text{Lu-PSMA617}</math></b>	<b>PSMA-</b>	475 $\pm$ 205 (225-765)	0.03 $\pm$ 0.01 (0.02-0.04)	0.04 $\pm$ 0.01 (0.04-0.05)
	<b>PSMA<sup>+</sup></b>	308 $\pm$ 66 (245-423)	0.06 $\pm$ 0.02 (0.03-0.08)	0.07 $\pm$ 0.02 (0.05-0.09)
	<b>PSMA<sup>++</sup></b>	209 $\pm$ 110 (91-411)	0.28 $\pm$ 0.05 (0.24-0.33)	0.15 $\pm$ 0.03 (0.12-0.17)
	<b>PSMA<sup>+++</sup></b>	103 $\pm$ 27 (50-138)	1.66 $\pm$ 0.23 (1.43-1.88)	0.30 $\pm$ 0.14 (0.18-0.45)
<b>2. Fraction PSMA positive cells in the RM1 model; <math>^{177}\text{Lu-PSMA617}</math></b>	<b>0%</b>	306 $\pm$ 110 (173-505)	0.07 $\pm$ 0.02 (0.05-0.08)	0.03 $\pm$ 0.01 (0.02-0.04)
	<b>25%</b>	195 $\pm$ 28 (150-230)	0.91 $\pm$ 0.13 (0.77-1.04)	0.09 $\pm$ 0.06 (0.05-0.15)
	<b>50%</b>	205 $\pm$ 54 (122-266)	0.99 $\pm$ 0.30 (0.65-1.23)	0.09 $\pm$ 0.04 (0.05-0.12)
	<b>75%</b>	146 $\pm$ 73 (83-282)	1.23 $\pm$ 0.07 (1.15-1.28)	0.14 $\pm$ 0.02 (0.12-0.15)
	<b>100%</b>	103 $\pm$ 22 (70-129)	1.36 $\pm$ 0.32 (1.15-1.73)	0.26 $\pm$ 0.14 (0.15-0.45)
<b>3. Fraction PSMA positive cells in the PC-3 model; <math>^{177}\text{Lu-PSMA617}</math></b>	<b>0%</b>	30.9 $\pm$ 2.6* (28.4-33.6)	0.02 $\pm$ 0.002 (0.02-0.03)	3.67 $\pm$ 0.84 (3.0-4.6)
	<b>33%</b>	29.9 $\pm$ 24.8* (4.8-79.3)	4.30 $\pm$ 1.19 (3.12-5.50)	6.01 $\pm$ 0.26 (5.7-6.3)
	<b>66%</b>	25.2 $\pm$ 2.5 (22.9-29.1)	7.24 $\pm$ 0.88 (6.39-8.15)	7.08 $\pm$ 1.83 (5.0-8.5)
	<b>100%</b>	0.4 $\pm$ 0.3 (0.11-1.2)	15.92 $\pm$ 1.11 (15.03-17.16)	14.57 $\pm$ 4.12 (10.0-18.1)
<b>4. Fraction PSMA positive cells in the RM1 model; <math>^{225}\text{Ac-PSMA617}</math></b>	<b>0%</b>	141 $\pm$ 54 (79-226)*	0.10 $\pm$ 0.01 (0.09-0.12)	5.15 $\pm$ 0.73 (4.35-5.80)
	<b>33%</b>	162 $\pm$ 23 (140-161)	1.64 $\pm$ 0.73 (0.91-2.37)	8.20 $\pm$ 1.87 (6.16-9.84)
	<b>66%</b>	112 $\pm$ 10 (104-127)	2.85 $\pm$ 0.30 (2.61-3.18)	11.42 $\pm$ 0.96 (10.56-12.46)
	<b>100%</b>	52 $\pm$ 9 (44-62)	4.66 $\pm$ 1.05 (3.83-5.84)	18.30 $\pm$ 4.77 (14.0-23.43)

\*Data represent relative tumor volumes on day 69 (0%, study 3), day 81 (33%, study 3), or day 17 (0%, study 4), because reaching humane endpoints decreased group sizes to  $n < 3$ .