^{177}Lu-PSMA-617 versus Docetaxel in Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer: A Randomized, Controlled, Phase 2 Non-inferiority Trial

Supplementary Material

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Supplementary Table 1: Eligibility criteria for patient accrual

Inclusion Criteria

• Biopsy proven adenocarcinoma prostate
• Castration resistant prostate cancer defined by castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:
  ○ Biochemical progression: Three consecutive rises in PSA one week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml.
  ○ Radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours.
• Metastatic disease (as established by ^{68}Ga –PSMA-11 PET/CT)
• Significant PSMA expression in ^{68}Ga –PSMA-11 PET/CT defined as tracer avidity of at least 80% of the lesions being significantly (≥1.5 times) greater than that of normal liver with none of the lesions having uptake less than that of liver
• Chemotherapy naive patients; patients with prior treatment of new generation antiandrogens will however be included
• ECOG performance 0-2
• Adequate renal function – Technetium-99m diethylenetriaminepentaacetate GFR ≥40 mL/min
• Stable haematological parameters:
  ○ Hemoglobin ≥ 9 g/dL
  ○ Neutrophils ≥ 1500/mcL
  ○ Platelets ≥ 75000/mcL
• Adequate liver function:
  ○ Bilirubin < 1.5 x ULN (or if bilirubin is between 1.5-2x ULN, must have a normal conjugated bilirubin)
  ○ Transaminases ≤ 1.5 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases)
  ○ Albumin ≥ 2.5 g/dL

Exclusion Criteria
• Prostate cancer with sarcomatous/spindle cell/small cell differentiation • PSMA expression in ^{68}Ga – PSMA PET/CT less than liver • Sjogren Syndrome • Prior treatment with Docetaxel/Cabazitaxel/^{177}Lu-PSMA RLT • Active malignancy other than prostate cancer • Concurrent illness, including severe infection • Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception
ECOG: Eastern Cooperative Oncology Group; GFR: Glomerular Filtration Rate; PSA: Prostate Specific Antigen; PSMA : Prostate Specific Membrane Antigen; RLT: Radioligand Therapy; ULN: Upper Limit of Normal

Supplementary Table 2: Subgroup analysis of efficacy end-points

Parameter	First-line therapy in mCRPC			≥Second-line therapy in mCRPC		
	^{177}Lu-PSMA-617 (N=6)	Docetaxel (N=8)	Difference (95% CI)	^{177}Lu-PSMA-617 (N=14)	Docetaxel (N=12)	Difference (95% CI)
Best PSA-RR, n/N (%)	3/6 (50%)	2/8 (25%)	25% (-21–61)	7/14 (50%)	6/12 (50%)	0% (-34–34)
ORR, n/N (%)	3/4 (75%)	3/7 (43%)	32% (-23–66)	2/9 (22%)	3/12 (25%)	3% (-33–35)
MRR, n/N (%)	2/4 (50%)	2/7 (29%)	21% (-28–62)	4/10 (40%)	4/12 (33%)	7% (-29–41)
PFS rate at 6 months (%)	33%	12.5%	20.5% (-21–58)	17%	25%	8% (-22–38)

CI: Confidence Intervals; mCRPC: Metastatic Castration-Resistant Prostate Cancer; MRR: Molecular Response Rate; ORR: Objective Radiological Response Rate; PFS: Progression-free Survival; PSA-RR: prostate specific antigen-response rate

Supplementary Table 3: Univariate and multivariate analysis of potential prognostic factors for progression-free survival

Parameter	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age	0.97 (0.93-1.01)	0.19	--	--
Gleason score≥8 versus <8	1.34 (0.64-2.79)	0.43	--	--
ECOG score ECOG 0 ECOG 1 ECOG 2	 1 0.73 (0.28-1.90) 0.85 (0.29-2.49)	0.82	-- -- -- --	-- -- -- --
Prior novel anti-androgens (Yes versus No)	1.03 (0.49-2.13)	0.94	--	--
Skeletal lesions ≥20 versus <20	1.13 (0.58-2.21)	0.72	--	--
Visceral metastasis (Yes versus No)	1.50 (0.69-3.26)	0.30	--	--
Baseline ALP	1.002 (1.000-1.003)	0.05	1.001 (1.000-1.003)	0.11
Baseline PSA	0.999 (0.998-1.001)	0.47	--	--
Treatment (^{177}Lu-PSMA-617 versus Docetaxel)	0·90 (0.46–1.77)	0.77	--	--
PSA decline ≥50% (No versus Yes)	3.71 (1.73-7.92)	<0.01	4.57 (1.74-11.95)	<0.01

ALP: Alkaline Phosphatase; CI: Confidence Intervals; ECOG: Eastern Cooperative Oncology Group; HR: Hazard Ratio; PSA: Prostate specific antigen

Supplementary Table 4: Post-study treatments in the two arms

Post-study Treatment	^{177}Lu-PSMA-617 arm (No.)	Docetaxel arm (No.)
Docetaxel	5	0
Abiraterone	1	3
Enzalutamide	2	9
^{177}Lu-PSMA-617	0	1
^{225}Ac-PSMA-617	1	0

Supplementary Table 5: Pre- and post-therapy health-related quality of life scores as measured with NCCN-FACT-FPSI-17 questionnaire

Scale (maximum score)	^{177}Lu-PSMA-617 arm (n=15)			Docetaxel arm (n=20)			p value[b]
	Pre-therapy score[a]	Post-therapy score[a]	Change in score from baseline[a]	Pre-therapy score[a]	Post-therapy score[a]	Change in score from baseline[a]	
DRS-P (40)	24 (14 – 27)	29 (17 – 33)	4 (-3 – 10)	27·5 (25 – 30)	25 (23 – 29)	-2 (-5 – 0·8)	**0·023**
DRS-E (4)	2 (1 – 4)	3 (2 – 4)	0 (0 – 2)	2 (1·25 – 3)	2 (2 – 3)	0 (-1 – 1)	**0·043**
TSE (16)	13 (10 – 15)	13 (12 – 15)	0 (0 – 1)	8 (7·25 – 9)	7 (5 – 7·8)	-2 (-4 – 0)	**0·001**
F/WB (8)	4 (2 – 7)	4 (3 – 7)	0 (0 – 1)	6 (3·2 – 8)	4 (4 – 7)	-0·5 (-3 – 1)	0·191
Total FPSI-17 (68)	41 (28 – 51)	49 (33 – 58)	7 (-4 – 15)	44 (39 – 50·5)	38 (31 – 45)	-8 (-11 – 1)	**0·003**

[a]Variables expressed as median and interquartile range (1st quartile – 3rd quartile)

[b]Comparison of median change in scores from baseline in the two arms: p value calculated using Mann-Whitney U test

DRS-E: Disease-related symptoms – emotional; DRS-P: Disease-related symptoms – physical; FPSI: FACT Prostate Symptom Index; F/WB: Function/well-being; TSE: Treatment side-effects

Supplementary Table 6: Efficacy end-points in patients with visceral metastases

Parameter	^{177}Lu-PSMA-617 arm (N=5)	Docetaxel arm (N=4)
Best PSA-RR, n/N (%)	1/5 (20%)	3/4 (75%)
ORR, n/N (%)	0/2 (0%)	2/4 (50%)
MRR, n/N (%)	0/2 (0%)	1/4 (25%)
PFS rate at 6 months (%)	0%	25%

MRR: Molecular Response Rate; ORR: Objective Radiological Response Rate; PFS: Progression-free Survival; PSA-RR: prostate specific antigen-response rate

Supplementary Fig.1: Waterfall plots describing the percentage changes in serum PSA values from baseline in intention-to-treat analysis. CI: confidence intervals; PSA = prostate specific antigen; PSMA = prostate specific membrane antigen