PCPro as a prognostic plasma lipidomic biomarker in TheraP (ANZUP 1603): a randomised trial of [177Lu]Lu-PSMA-617 (LuPSMA) vs cabazitaxel in metastatic castration resistant prostate cancer (mCRPC)

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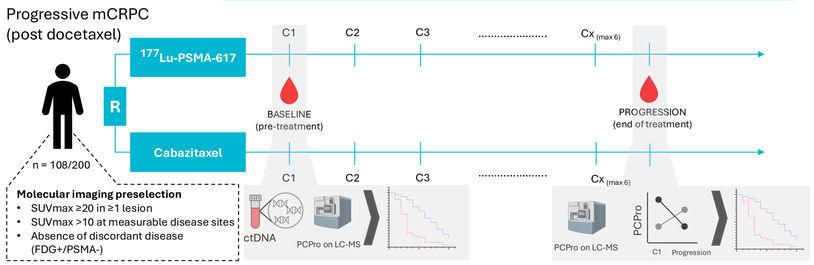
Background

- Lutetium-177[^{177}Lu]Lu-PSMA-617 is a recently established standard-of-care therapy in patients with metastatic castration-resistant prostate cancer (mCRPC).
- The TheraP trial showed that LuPSMA improves PSA response rate (RR), objective tumour RR and radiographic progression free survival (rPFS), compared with cabazitaxel in people with PSMA-positive, non-FDG-discordant mCRPC progressing after docetaxel.[1,2]
- Elevated circulating sphingolipids, including ceramides, are associated with shorter PFS and OS in mCRPC treated with docetaxel or ARPIs.[3]
- PCPro is a validated, plasma lipid biomarker, developed in accordance with CLIA/NATA guidelines, comprising Ceramides: Cer(d18:1/18:0), Cer(d18:1/24:0), Cer(d18:1/24:1), total cholesterol and triglycerides.[4]
- PCPro positive patients with mCRPC have shorter rPFS and overall survival (OS) when treated with ARPIs and shorter OS when treated with docetaxel.
- Quantitative PET/CT and ctDNA biomarkers have demonstrated predictive and prognostic capability.[5,6]
- This is the first report of the association of PCPro status with clinical outcomes in people treated with LuPSMA or cabazitaxel.

Study Design

Study Aims

1. Describe the association between PCPro with clinical outcomes in participants treated with LuPSMA or cabazitaxel in the TheraP study
2. Evaluate the association of PCPro with established molecular imaging prognostic thresholds and ctDNA% categories



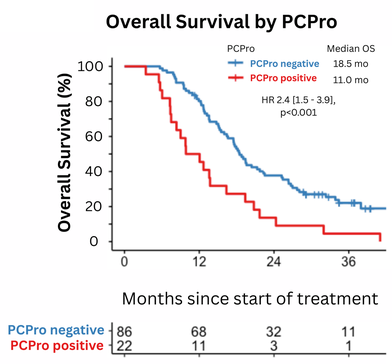
Patient Characteristics

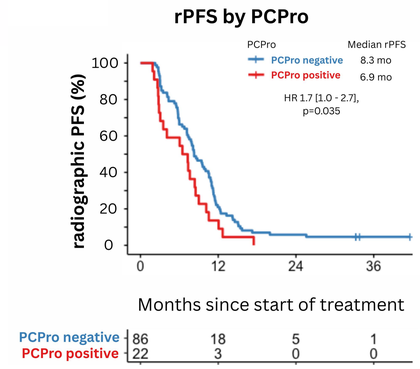
	LuPSMA (biomarker cohort) (n=60)	Cabazitaxel (biomarker cohort) (n=49)	LuPSMA (whole cohort) (n=99)	Cabazitaxel (whole cohort) (n=101)
Age, median (IQR)	72 (67 – 76)	72 (68 – 76)	72 (67 – 77)	72 (67 – 77)
> 20 metastases*, n (%)	45 (75)	38 (78)	77 (78)	79 (78)
ECOG, N (%)				
0	30 (50)	29 (59)	42 (42)	44 (44)
1-2	30 (50)	20 (42)	57 (58)	56 (55)
Unknown	0	0	0	1 (1)
PSA (ng/mL), median (IQR)	73.6 (38.5-128.15)	95.3 (34.7-230)	93.5 (44-219)	110 (64-245)
Alkaline phosphatase (U/L), median (IQR)	112 (88-174)	133 (83-190)	111 (83-199)	130 (79-187)
Disease location, n (%)				
Lymph node only	6 (10)	5 (10)	7 (7)	9 (9)
Bone metastases	52 (87)	43 (88)	90 (91)	90 (89)
Visceral metastases	4 (7)	4 (8)	7 (7)	13 (13)
Previous ARPI, n (%)				
Abiraterone only	15 (25)	13 (27)	21 (21)	24 (24)
Enzalutamide only	12 (20)	4 (8)	49 (50)	58 (57)
Both	29 (48)	27 (55)	21 (21)	9 (9)
PSMA SUVmean, median (IQR)	9.0 (7.1-11.7)	8.5 (6.9-10.2)	8.5 (7.1-11.5)	8.5 (6.8-10.5)
FDG-PET MTV (mL), median (IQR)	101.5 (29.8-266.3)	66.6 (14.3-224)	100 (23-252.5)	78 (22-248)
PSMA SUVmean ≥10, n (%)	22 (37)	15 (31)	37 (37)	33 (33)
FDG MTV ≥200mL, n (%)	19 (32)	13 (27)	31 (31)	30 (30)
Median rPFS, months (95% CI)	8.43 (7.29 – 9.53)	7.89 (7.36 – 8.57)	8.51 (6.47 – 10.97)	7.95 (7.20 – 9.13)
HR rPFS (95% CI), p value	0.78 (0.59 – 1.03), p=0.075		0.68 (0.50 – 0.93), p=0.015	
Median OS, months (95% CI)	16.4 (13.7 – 21.2)	18.4 (15.5 – 24.3)	16.36 (13.73 – 19.58)	19.42 (15.51 – 23.06)
HR OS (95% CI), p value	0.98 (0.64 – 1.49), p=0.9		0.98 (0.71 – 1.36), p=0.9	

Table 1: Patient characteristics of biomarker and trial cohorts

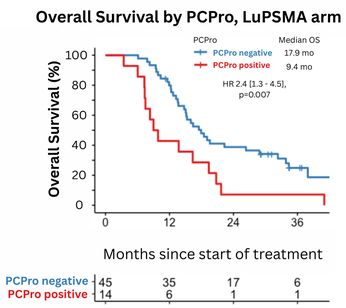
* Disease burden as assessed by [^{68}G1]Ga-PSMA-11

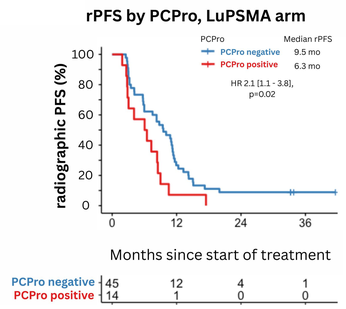
PCPro is prognostic for OS and rPFS

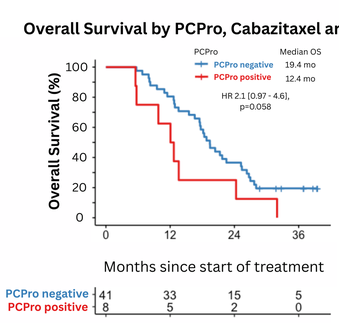


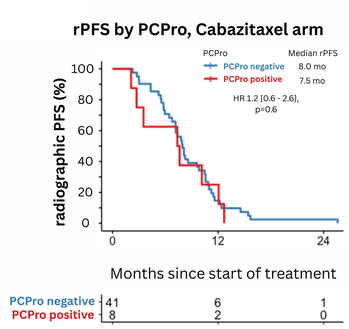


PCPro is prognostic independent of treatment arm









Variable	Hazard Ratio OS [95% CI], p value	Interaction variable p value OS	Hazard Ratio rPFS [95% CI], p value	Interaction variable p value, rPFS
PCPro, positive	2.40 [1.47-3.92], p<0.001	**0.8**	1.67 [1.04 – 2.68], p=0.034	**0.2**
Treatment arm, LuPSMA	0.92 [0.60 – 1.41], p=0.8		0.78 [0.53 – 1.15], p=0.2	

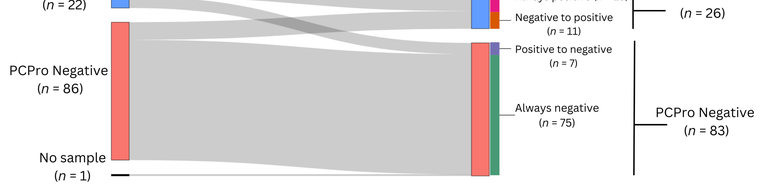
Table 2: Bivariable Cox regression of PCPro and Treatment arm

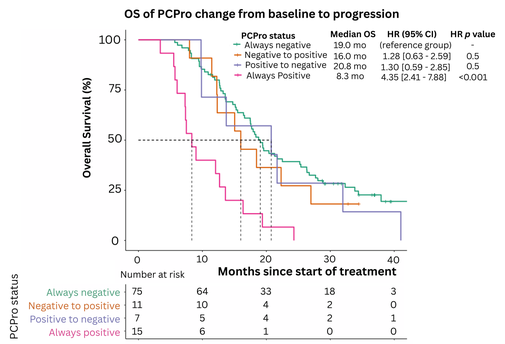
PCPro is prognostic independent of other prognostic biomarkers

Variable	Hazard Ratio OS [95% CI]	OS *p* value
PCPro, positive	1.78 [1.05 – 3.03]	0.032
PSMA PET SUV mean <10	1.39 [0.82 – 2.34]	0.2
FDG PET Mean Tumour Volume ≥ 200	2.29 [1.40 – 3.75]	0.001
ctDNA fraction	(Reference)	(Reference)
ctDNA 2-30%	4.07 [1.55 – 10.7]	0.004
ctDNA >30%	8.91 [3.17 – 25.1]	<0.001

Table 3: Multivariable analysis for PCPro with other prognostic variables for OS

Patients who remain PCPro positive at progression have the worst prognosis





Conclusions

- **PCPro positive status was an independently significant prognostic factor for shorter OS and rPFS in participants treated in the TheraP trial with either LuPSMA or cabazitaxel**
- **Participants who remained PCPro positive at baseline and at progression had the worst prognosis**
- **These data support further research of PCPro as a prognostic biomarker in people with mCRPC being treated with LuPSMA or taxane chemotherapy.**

References

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More Information

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in collaboration with

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Conflicts of interest

Dr Tahlia Scheinberg is a co-inventor of the patent for PCPro, licensed by Chris O'Brien Lifehouse (PCT/AU2023/050849). She has received conference travel support from Bayer.

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