Plasma lipidomics and PCPro as prognostic biomarkers 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: The TheraP trial demonstrated that LuPSMA improved PSA response rates and radiographic progression-free survival (rPFS) compared to cabazitaxel in participants with PSMA-positive, non-FDG-discordant mCRPC progressing post docetaxel.

Elevated circulating sphingolipids, especially ceramides, are associated with shorter rPFS and overall survival (OS) in patients with mCRPC treated with androgen receptor pathway inhibitors (ARPI) or docetaxel. PCPro is a validated, CLIA/NATA compliant plasma lipid biomarker, comprising Ceramide(d18:1/18:0), Ceramide(d18:1/24:0), Ceramide(d18:1/24:1), total cholesterol and triglycerides, capable of prospectively identifying people with mCRPC and ARPI or docetaxel resistance (shorter rPFS and OS when treated with ARPI; shorter OS when treated with docetaxel). We report the association of lipidomic changes and PCPro status with clinical outcomes in patients treated with either LuPSMA or cabazitaxel.

Methods:

Baseline and progression plasma from 109/200 (54%) TheraP participants were profiled by liquid chromatography-mass spectrometry for comprehensive lipidomic profiling and PCPro. Associations with rPFS and OS were assessed by Kaplan-Meier and Cox regression methods.

Results:

819 lipids across 23 classes were detected in the plasma of TheraP participants, predominantly phosphatidylcholine (27.59%), triglyceride (15.87%), phosphatidylethanolamine (14.57%) and ceramide (12.58%). Univariate Cox regression identified 92 lipids significantly associated with rPFS and 88 with OS ($p<0.05$). Several overlapped with the 46 prognostic lipids previously reported in mCRPC. Ceramide(d18:1/24:1), a sphingolipid and component of the PCPro signature, demonstrated the strongest prognostic value. It was the only lipid to remain significant in multivariate analysis for both rPFS (HR 2.36, 95% CI 1.39–3.99, p=0.0014) and OS (HR 2.23, 95% CI 1.19–4.17, p=0.0125).

22/108 participants (20%) were PCPro-positive. These individuals had significantly shorter rPFS (HR 1.7, 95% CI 1.04–2.7, p=0.035) and OS (HR 2.4, 95% CI 1.5–3.9, p=0.001) compared to PCPro-negative participants. PCPro-positivity was observed in 14/59 (24%) participants treated with LuPSMA and 8/49 (16%) treated with cabazitaxel. The prognostic significance of PCPro for rPFS and OS was independent of the treatment arm (interaction p value OS=0.8, rPFS=0.2). PCPro remained an independently significant prognostic factor for OS in a model accounting for other prognostic factors (Table 1).

Participants who remained PCPro-positive at both baseline and progression had the worst prognosis (median OS: always-positive 8.3months, always-negative 19.0months; HR 4.35, 95% CI 2.41–7.88, $p<0.001$). There was no difference in OS between participants who were PCPro-positive at baseline but became PCPro-negative at progression and those who were always PCPro-negative (median OS: positive-to-negative 20.8months; HR 1.30 , 95% CI 0.59–2.85, p=0.5).

Conclusions:

PCPro-positive status is an independent prognostic factor for shorter OS in mCRPC patients treated with LuPSMA or cabazitaxel. Conversion from PCPro-positive to negative is associated with improved outcomes, suggesting that dynamic lipidomic changes may reflect treatment response. These findings highlight sphingolipid metabolism as a potential therapeutic target in treatment-resistant mCRPC.

Table 1. Multivariable analysis for OS

Variable	Hazard ratio (95% confidence interval)	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	-	-
ctDNA 2-30%	4.07 [1.55 – 10.7]	0.004
ctDNA >30%	8.91 [3.17 – 25.1]	<0.001

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Conflicts of Interest Disclosure:

Tahlia Scheinberg, Hui-Ming Lin, Peter Meikle and Lisa Horvath are co-inventors of a patent for PCPro licensed by Chris O'Brien Lifehouse.

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