Circulating tumour DNA fraction as a predictor of treatment efficacy in a randomized phase 2 trial of [^{177}Lu]Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603)

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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 (NCT03392428) showed that in patients with high-PSMA, non-FDG-discordant mCRPC progressing after docetaxel, ^{177}Lu-PSMA-617 improved biochemical response rates, progression-free survival and quality of life compared to cabazitaxel.[1,2]
- We present an exploratory analysis of circulating tumour DNA fraction (ctDNA%) in baseline samples from the TheraP trial.

Study design

Aims
- Associate validated ctDNA% categories[3] with established molecular imaging prognostic thresholds[4]
- Correlate ctDNA% with clinical outcomes (PSA response, progression-free survival [PFS])

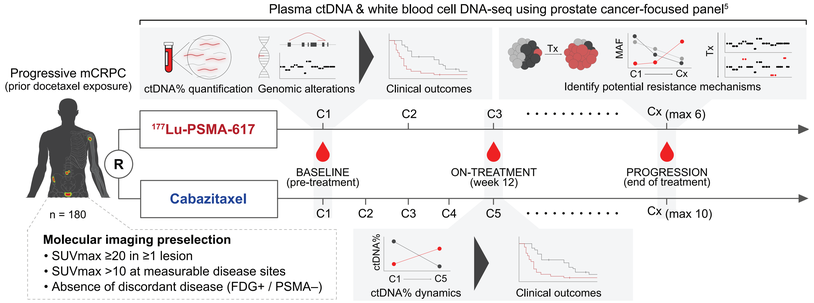

Figure 1: Overview of planned TheraP ctDNA genomics analysis.

Patient characteristics

	LuPSMA (N=97)	Cabazitaxel (N=83)
Age, median (IQR)	72 (66-78)	72 (67-75)
Disease burden*, N (%)		
> 20 metastases	76 (78)	63 (76)
≤ 20 metastases	21 (22)	20 (24)
ECOG, N (%)		
0 or unknown	45 (46)	41 (48)
1-2	52 (54)	40 (49)
PSA (ng/mL), median (IQR)	92 (44-200)	98 (62-276)
ALP (U/L), median (IQR)	110 (83-186)	130 (81-181)
Disease extent, N (%)		
Lymph node only	7 (7)	8 (10)
Bone metastases	88 (91)	74 (89)
Visceral metastases	7 (7)	10 (12)
Previous ARPI, N (%)		
Abiraterone only	20 (21)	22 (27)
Enzalutamide only	48 (49)	45 (54)
Both	21 (22)	7 (8)
Neither	8 (8)	9 (11)
PSMA SUVmean, median (IQR)	8.5 (7.0-12)	8.5 (6.6-11)
FDG-PET MTV (mL), median (IQR)	85 (23-230)	71 (20-221)
PSMA SUVmean ≥10, N (%)	35 (36)	23 (28)
FDG MTV ≥200 mL, N (%)	28 (29)	22 (27)
Median PFS, months (95% CI)	5.1 (3.5-6.5)	4.5 (2.9-6.0)
HR PFS (95% CI), *p* value	0.62 (0.46-0.86), 0.0033	

Table 1: Patient characteristics of biomarker population. *Disease burden as assessed by [^{68}Ga]Ga-PSMA-11.

ctDNA% selects distinct molecular imaging phenotypes

- We examined baseline samples from 180 patients who received ≥1 cycle of protocol-assigned treatment; two samples failed sequencing and were excluded from outcomes analyses.
- ctDNA was detected (defined as ≥2%) in 84% (150/178); median ctDNA was 24% (28% in ctDNA-detected subgroup) and balanced across treatment arms (**Fig. 2A**).
- Higher ctDNA% categories were enriched for patients with high FDG metabolic tumour volume (MTV) and low PSMA SUVmean disease (**Fig. 2B**).

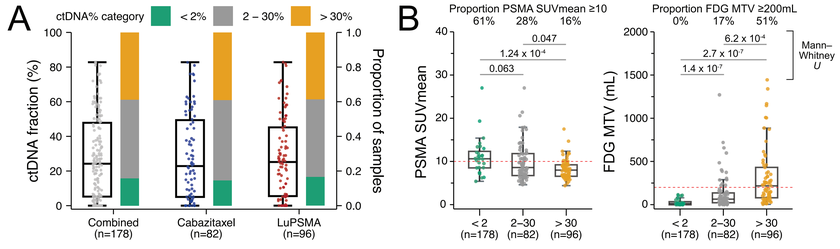

Figure 2: (A) ctDNA% in 178 baseline plasma samples. (B) Distribution of PSMA SUVmean and FDG MTV stratified by prespecified ctDNA% categories. P values reflect Mann-Whitney *U* tests and are two-sided.

LuPSMA demonstrates greater activity in patients with low ctDNA%

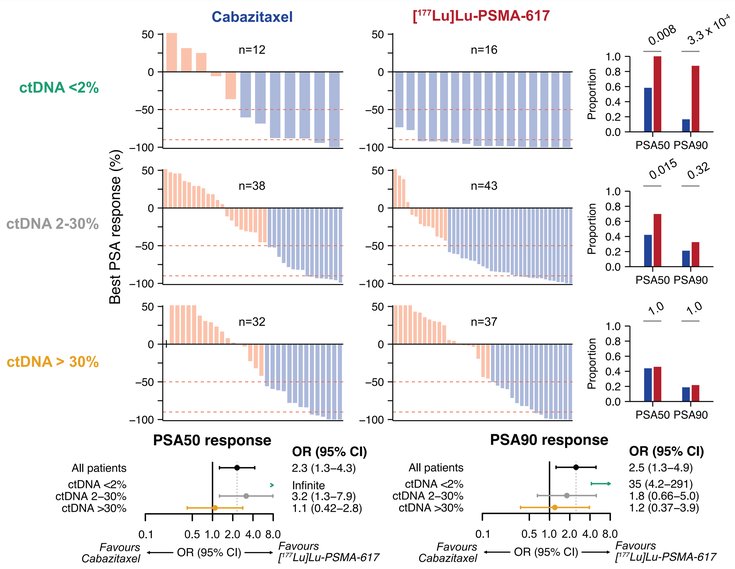

Figure 3: Biochemical outcomes (PSA50 and PSA90 response) stratified by ctDNA% categories.

Undetected ctDNA is predictive for superior PFS on LuPSMA vs cabazitaxel

- Patients with undetected ctDNA disproportionately benefited from LuPSMA compared with cabazitaxel, with a marked increase in biochemical response (**Fig. 3**) and a 8.7 month increase in median PFS (HR 0.12, $p = 2.5\times10^{-4}$; **Fig. 4A-B**).
- Undetected ctDNA remained independently predictive for superior PFS on LuPSMA versus cabazitaxel in a multivariable analysis incorporating baseline PSMA SUVmean and established clinical prognostic factors (HR 0.35, 95% CI 0.13-0.93; interaction $p = 0.035$).
- Combining ctDNA detection with PSMA SUVmean further stratified outcomes in patients receiving LuPSMA (**Fig. 4C**).

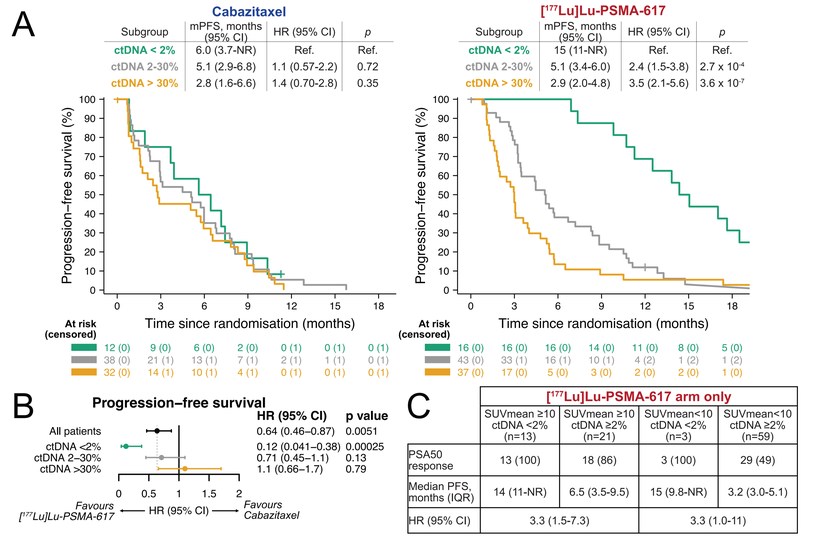

Figure 4: (A) Kaplan-Meier estimates of PFS stratified by treatment arm and ctDNA% categories. (B) Forest plot by ctDNA% categories for PFS. (C) PSA and PFS outcomes combining PSMA SUVmean ≥10 and ctDNA detectability.

Conclusions

- ctDNA% is associated with FDG tumour burden and PSMA expression in mCRPC, and could serve as a adjunctive tool to aid patient selection for PSMA radioligand therapy.
- ctDNA% is a candidate predictive and prognostic biomarker for differential response to LuPSMA *vs* cabazitaxel in patients with molecular imaging-selected mCRPC progressing after docetaxel.
- These findings are exploratory and require validation in independent cohorts.

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Contribution† | EMK, MSH and SWSN contributed equally to this work.

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