Baseline ctDNA analyses and associations with outcomes in taxane-naive patients with mCRPC treated with ^{177}Lu-PSMA-617 versus change of ARPI in PSMAfore

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Background

[^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolonged radiographic progression-free survival (rPFS) versus androgen receptor pathway inhibitor (ARPI) change in taxane-naive patients with metastatic castration-resistant prostate cancer (mCRPC) in PSMAfore (NCT04689828). In this exploratory analysis, associations between baseline circulating tumor DNA (ctDNA) and outcomes were assessed.

Methods

Patients were randomized 1:1 to ^{177}Lu-PSMA-617 (7.4 GBq Q6W; 6 cycles) or ARPI change (abiraterone/enzalutamide). Patients known to have actionable mutations (e.g. *BRCA*) were excluded. The primary endpoint was rPFS. Baseline plasma ctDNA was analyzed using a customized 585-gene sequencing assay. ctDNA fraction was assessed in all samples passing quality control. Alterations in key prostate cancer drivers (prevalent in >10% participants) were assessed in samples with ctDNA fraction >1%. Univariate Cox regression (reference: ARPI change) was used to assess association of ctDNA fraction or alterations with rPFS, prostate-specific antigen response (≥50% decline; PSA50) and RECIST response (RR) at the June 21, 2023 data cutoff.

Results

Of 360 samples from 468 patients, 255 passed quality control and 156 had ctDNA fraction >1% (median 5.85%; range 0–85). Detection of ctDNA alterations was comparable between arms and with published data. Median rPFS was shorter for patients with ctDNA fraction > versus ≤1% (HR 2.753; 95% CI 1.957–3.872; $p<0.0001$) (**Table**); ctDNA fraction >1% was also associated with worse RR and PSA50 response. Median rPFS was shorter for patients with detected versus undetected *AR* (HR 1.954; 95% CI 1.333–2.865; $p<0.001$), *TP53* (1.655; 1.13–2.426; $p<0.01$) and *PTEN* (1.62; 1.018–2.578; $p<0.05$) alterations. Median rPFS was longer with ^{177}Lu-PSMA-617 versus ARPI change in patients with detected *AR*, *TP53, PTEN* (**Table**)*,* PI3K pathway and DNA repair pathway alterations. There was no significant association between ctDNA alterations and PSA50 or RR.

Conclusions

ctDNA fraction >1% and *AR*, *TP53* and *PTEN* alterations were associated with worse outcomes in PSMAfore regardless of treatment. Nonetheless, patients with these negative prognostic biomarkers did better with ^{177}Lu-PSMA-617 than with ARPI change.

Table

	^{177}Lu-PSMA-617	**ARPI change**	**^{177}Lu-PSMA-617**	**ARPI change**	**^{177}Lu-PSMA-617**	**ARPI change**
	Median rPFS, mos (95% CI)		**PSA50 non-responders (<50% decline), n**		**RR non-responders, n**	
ctDNA fraction > v ≤1%	**N=120**	**N=153**	**N=49**	**N=88**	**N=28**	**N=52**
	7.9 (5.8–11.3) v 17.1 (11.5–NE)	2.4 (2.3–4.2) v 6.0 (5.6–13.7)	32 v 17	53 v 35	20 v 8	35 v 17
Alteration detected v undetected	**N=74**	**N=82**	**N=32**	**N=53**	**N=20**	**N=35**
AR	5.0 (2.7–8.6) v 11.6 (6.2–NE)	2.3 (2.1–5.6) v 2.7 (2.2–6.0)	13 v 19	20 v 33	9 v 11	15 v 20
TP53	6.1 (3.1–9.3) v 9.2 (6.2–NE)	2.4 (2.2–4.3) v 2.7 (2.3–5.8)	12 v 20	22 v 31	8 v 12	15 v 20
PTEN	3.6 (2.5–NE) v 7.9 (6.1–11.6)	2.1 (2.0–NE) v 3.1 (2.3–5.8)	7 v 25	10 v 43	4 v 16	8 v 27

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