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

Edmond M. Kwan[a,b,j], Michael S. Hofman[c,j], Sarah W.S. Ng[a], Louise Emmett[d,j], Shahneen Sandhu[c,j], James P. Buteau[c,j], Amir Iravani[c,j], Anthony M. Joshua[d,j], Roslyn J. Francis[e,j], Vinod Subhash[j], Sze-Ting Lee[f,j], Andrew M. Scott[f,j], Andrew J. Martin[g,j], Martin R. Stockler[g,j], Grainne Donnellan[a], Matti Annala[h], Sofie H. Tolmeijer[a], Arun A. Azad[c,j], Ian D. Davis[b,i,j], Alexander W. Wyatt[a], on behalf of the TheraP Investigators and the ANZUP Cancer Trials Group[j].

[a]Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, BC, Canada. [b]Monash University, Melbourne, VIC, Australia. [c]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. [d]St Vincent's Hospital, Sydney, NSW, Australia. [e]Sir Charles Gairdner Hospital, Perth, WA, Australia. [f]Austin Health, Melbourne, VIC, Australia. [g]NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia. [h]Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Centre, Tampere, Finland. [i]Eastern Health, Melbourne, VIC, Australia. [j]Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP), Sydney, NSW, Australia.

Background

The TheraP trial (NCT03392428) showed that for patients with PSMA-positive, non-FDG-discordant mCRPC progressing after docetaxel, LuPSMA significantly improved biochemical and objective response rates, progression-free survival (PFS), and quality of life compared to cabazitaxel. While subsequent studies nominated high PSMA SUVmean to inform patient prioritization for LuPSMA, limited genomic data exists to guide optimal selection of these two life-prolonging therapies. We present an exploratory analysis of ctDNA fraction (ctDNA%) in baseline samples from the TheraP trial.

Methods

We analyzed 180 baseline blood samples from participants who received ≥1 cycle of protocol-assigned treatment. Plasma cell-free DNA and matched white blood cell DNA underwent targeted sequencing to estimate ctDNA%. Prespecified ctDNA% categories (<2%, 2-30%, and >30%) were associated with previously validated imaging thresholds (PSMA SUVmean ≥10 and FDG metabolic tumor volume [MTV] ≥200mL), rate of PSA reduction ≥50% (PSA50-RR), and PFS, using chi-square test, logistic regression and Cox regression, respectively.

Results

ctDNA% was evaluable in 178 (99%) participants, with ctDNA ≥2% in 85%. Median ctDNA% was 28% in ctDNA≥2% samples, and balanced across treatment arms. The odds of a PSA50 response to LuPSMA *vs* cabazitaxel were significantly higher for men with ctDNA <2% (OR infinite, p=0.008; PSA50-RR 100% *vs* 58%), with no difference at ctDNA >30% (OR 1.1, p=1.0; PSA50-RR 46% *vs* 44%). Higher ctDNA% was associated with shorter PFS in LuPSMA- but not cabazitaxel-treated patients (LuPSMA: HR 5.1, p<0.001 for ctDNA >30% *vs* <2%; cabazitaxel: HR 1.4, p=0.35 for ctDNA >30% *vs* <2%; interaction p=0.032). The predictive potential of ctDNA% was additive to PSMA SUVmean in LuPSMA-treated patients. Higher ctDNA% categories were enriched for patients with high FDG MTV and low PSMA SUVmean disease (**Table**).

Conclusions

ctDNA% is a candidate predictive and prognostic biomarker for differential response to LuPSMA versus taxane chemotherapy in patients with molecular imaging-selected mCRPC progressing after docetaxel.

	LuPSMA (ctDNA categories)			Cabazitaxel (ctDNA categories)			LuPSMA (PSMA SUVmean and ctDNA category)			
	<2% (n=16)	2-30% (n=43)	>30% (n=37)	<2% (n=12)	2-30% (n=38)	>30% (n=32)	≥10 + <2% (n=13)	<10 + <2% (n=3)	≥10 + ≥2% (n=21)	<10 + ≥2% (n=58)
PSA50-RR	100%	70%	46%	58%	42%	44%	100%	100%	86%	49%
Odds ratio (LuPSMA *vs* cabazitaxel)	<2%: OR infinite, *p*=0.008 2-30%: OR 3.2, *p*=0.015 >30%: OR 1.1, *p*=1.0									
Median PFS (mo)	15	5.1	2.9	6.0	5.1	2.8	14	15	6.5	3.2
HR (95% CI)	Ref	3.0 (1.6-5.7)	5.1 (2.7-9.7)	Ref	1.1 (0.57-2.2)	1.4 (0.70-2.8)	Ref	1.3 (0.35-4.5)	2.7 (1.2-5.7)	4.7 (2.4-9.2)
FDG MTV ≥200mL	0%	23%	46%	0%	11%	56%				
p	<0.001			<0.001						
PSMA SUVmean ≥10	81%	35%	16%	33%	37%	16%				
p	<0.001			0.13						

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