Blood and imaging response correlatives in advanced prostate cancer treated with combination radioligand and immunotherapy

Sofie H. Tolmeijer[1], Edmond M. Kwan[1], Andrei Gafita[2], Sarah W.S. Ng[1], Anthony M. Joshua[3], Louise Emmett[4], Megan Crumbaker[3], Anis A. Hamid[5], Arsha Anton[6], Lisa G. Horvath[7], Joanna Chan[8], Mathias Bressel[9], James P. Buteau[10], Nattakarn Dhiantravan[11], Narjess Ayati[4], Shivakumar Keerthikumar[8], David L. Goode[8], Rodney J. Hicks[12], Michael S. Hofman[10], Alexander W. Wyatt[1], Shahneen Sandhu[13]

[1] Department of Urologic Sciences, Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada; [2] Division of Nuclear Medicine and Molecular Imaging, The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3] Medical Oncology, St Vincent's Hospital, Darlinghust, NSW, Australia; [4] Department of Nuclear Medicine & Theranostics, St Vincent's Hospital, Darlinghurst, NSW, Australia; [5] Medical Oncology, Memorial Sloan Cancer Center, New York, NY, USA, [6] Australia and Eastern Clinical Research Unit, Eastern Health, Monash University, Box Hill, Australia; [7] Medical Oncology, Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [8] Cancer Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia; [9] Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Center, Melbourne, Australia; [10] Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia; [11] Cancer Imaging, Peter MacCallum Cancer Center, Melbourne, VIC, Australia, [12] St Vincent's Medical School, The University of Melbourne, Parkville, Australia; [13] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

BACKGROUND: The PRINCE trial (NCT03658447) showed promising activity for radioligand [177Lu]Lu-PSMA-617 (LuPSMA) in combination with pembrolizumab, an anti-programmed death 1 inhibitor, in metastatic castration resistant prostate cancer. Here, we present an exploratory analysis of serial circulating tumor DNA (ctDNA) measurements with paired circulating tumor cell (CTCs) evaluations and PSMA-PET imaging to identify predictors of response and resistance to LuPSMA plus pembrolizumab.

METHODS: We analyzed plasma ctDNA, CTCs and PSMA-PET imaging for participants in the PRINCE trial at baseline (n=37), after 12 weeks of treatment (n=35) and at progression (n=28). FDG-PET imaging was available for all patients at baseline. Targeted sequencing of plasma and matched white blood cell DNA was used to estimate ctDNA fractions and assess genomic profiles. CTCs were quantified and single cell sequencing was performed using the EpicSciences platform. On-treatment changes on PSMA-PET imaging were assessed with RECIP criteria. Biomarkers at baseline and on-treatment were associated with PSA90 response rate (PSA90-RR) and radiographic progression free survival (rPFS).

RESULTS: Participants with baseline ctDNA fraction <30% or PSMA-PET SUVmean ≥10 showed superior rPFS, with potential complementary roles for both markers to enhance prognostic accuracy (n=12; median rPFS not-reached). Alterations in tumor suppressor genes (*TP53, RB1, PTEN*) detected in ctDNA were associated with greater FDG-PET SUVmean expression (5.6 vs 4.2, p=0.02), higher metabolic tumor volume (145.0 vs 30.3, p=0.004), and worse rPFS (3.9 vs 14.2 months, p<0.01) compared to patients without these alterations. Both ctDNA detection and PSMA-PET RECIP classification at 12-weeks on-treatment were strongly linked with PSA90-RR and rPFS. PSA90-RR and rPFS was similar for patients with undetected ctDNA regardless of RECIP classification. Participants with detected ctDNA at 12-weeks and progressive disease by RECIP had a shorter rPFS than those with stable disease by RECIP (median 2.9 vs 8.8 months, p<0.01). At progression, PSMA expression on PET-imaging was lower compared to baseline (PSMA SUVmean 5.8 vs 9.0, p<0.01), despite similar PSMA total tumor volumes and wildtype *FOLH1* ctDNA in all but one patient. Evidence for substantial subclonal remodeling was observed in ctDNA at progression and corroborated by single CTC copy number profiles. 24% of participants had a clonal expansion of tumor suppressor gene mutations at progression.

CONCLUSIONS: We propose that liquid biopsies have additive value to PET-imaging for patient prognostication and early treatment monitoring on LuPSMA plus pembrolizumab. Additionally, we provide new insights into molecular determinants of response and resistance to these agents, including ctDNA fraction, PSMA expression and tumor suppressor gene loss.

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