Combined Radium-223 and Lutetium-177 PSMA-I&T in patients with metastatic castration-resistant prostate cancer: first analysis of the single-center phase I/II AlphaBet trial

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Background
Lutetium-177 PSMA-I&T (LuPSMA) and Radium-223 (223Ra) are approved life-prolonging therapies for patients with metastatic castration-resistant prostate cancer (mCRPC); however, resistance and progression – particularly in bone - are common. We evaluated LuPSMA in combination with 223Ra, a bone-seeking alpha emitter, in patients with mCRPC.

Methods
We conducted a single-center, single-arm, investigator-initiated phase I/II trial sponsored by the Peter MacCallum Cancer Centre. Key eligibility criteria included progressive mCRPC with ≥2 untreated bone metastases, PSMA-PET positive disease (SUVmax ≥20) with no discordance (FDG- positive with minimal PSMA and bone scan uptake), and prior exposure to ≥1 androgen receptor pathway inhibitor. Patients received 223Ra and 7.4 GBq LuPSMA IV 6-weekly, for up to 6 cycles. Two dose levels of 223Ra (27.5 and 55 KBq/kg) were evaluated. Co-primary endpoints were determining the maximum tolerated dose (MTD), recommended phase II dose (RP2D), and PSA response rates. Key secondary endpoints included safety, PSA progression-free survival (PSA- PFS), radiographic PFS (rPFS), and overall survival (OS). ClinicalTrials.gov: NCT05383079

Results
Between 03 Nov 2022 and 05 Nov 2024, 36 patients were enrolled. Median (IQR) age was 72.5 years (67.0-78.0), baseline PSA 22 ng/mL (5.8-113.0), and ALP 111.5 U/L (81.5-157.2). 19 patients (53%) received prior docetaxel. No dose-limiting toxicities were observed. The MTD and RP2D was 55 KBq/kg 223Ra with 7.4 GBq LuPSMA. 11 pts (31%) received 6 cycles of both 223Ra and LuPSMA. Grade ≥3 treatment-related adverse events occurred in 14 patients (39%) and included anemia (n=4), neutropenia (n=3) and lymphopenia (n=10). 4 patients (11%) experienced grade 2 thrombocytopenia. No treatment-related deaths occurred. PSA50 and PSA90 response rates were 55% (95% CI 36–72) and 18% (7–35), respectively. Median PSA-PFS, rPFS, and OS were 5.3 (95% CI 4.0–9.0), 10.0 (6.7– 13.5), and 13.5 months (9.9–NE), respectively; with a median follow-up time of 13.3 months.

Conclusions
The combination of LuPSMA and 223Ra is safe and well-tolerated, demonstrating antitumor activity in patients with progressive mCRPC and bone metastases. The findings support further evaluation of combined alpha/beta-emitting approaches.

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Conflicts of Interest Disclosure Statement
Bayer provided institutional funding and radium-223 supply