

Circulating tumor DNA assessments for response to ¹⁷⁷Lu-PSMA-617 with ipilimumab and nivolumab in metastatic prostate cancer: results from the randomized phase II EVOLUTION trial (ANZUP 2001)

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BACKGROUND: EVOLUTION (NCT03658447, ANZUP 2001) showed promising activity of radioligand therapy with [¹⁷⁷Lu]Lu-PSMA-617 (LuPSMA) in combination with immune checkpoint inhibitors (ICI) ipilimumab and nivolumab in metastatic castration resistant prostate cancer. Here, we present an exploratory analysis of circulating tumor DNA (ctDNA) quantification and genomic interrogation to identify predictors of response and resistance to LuPSMA with dual ICI.

METHODS: We studied 87 participants (pts) in the intention to treat population of EVOLUTION: 30 assigned LuPSMA-alone and 57 LuPSMA with dual ICI. Baseline plasma ctDNA was available for 30/30 pts assigned LuPSMA and 54/57 assigned LuPSMA with dual ICI. Targeted sequencing of plasma and matched white blood cell DNA was used to estimate ctDNA fraction and assess genomic profiles (examining pre-specified thresholds and genes). Baseline ctDNA variables were associated with PSA reduction of 50% from baseline PSA50 response rate (PSA50-RR), PSA-progression free survival (PSA-PFS), radiographic-progression free survival (rPFS), and overall survival (OS).

RESULTS: Baseline ctDNA was quantified $\geq 2\%$ for 59/84 (70%) pts. Median fraction was 6.8% and not different between treatment arms ($p=0.5$). In all 87 pts, those with ctDNA $< 2\%$ had a longer OS than those with ctDNA $\geq 2\%$ (medians 29 vs 17 months, $p=0.008$). When split by treatment arm, a difference in OS was observed for low ctDNA vs high ctDNA in the LuPSMA arm (median not reached vs 15 months, HR 1.5, 95%CI 1.3-15.9, $p=0.01$) but not the combination arm (medians 26 vs 21 months, HR 1.7, 95%CI 0.8-3.7, $p=0.2$), with similar survival for participants ctDNA $< 2\%$ regardless of addition of dual ICI. 16 pts had a DNA damage repair alteration: 5 with *BRCA2*, 5 *ATM*, 5 *CDK12* and 1 mismatch repair deficiency. Longer rPFS and OS were observed for those with a DDR alteration assigned LuPSMA with dual ICI rather than LuPSMA-alone (median rPFS 5 vs 15 months, HR 0.04, 95% CI 0.004-0.4, $p=0.007$; median OS 23 vs 13 months, HR 0.1, 95%CI 0.02-0.7, $p=0.02$). Alterations in *TP53* were observed in 31 pts and associated with poor prognosis regardless of treatment group.

CONCLUSIONS: ctDNA $< 2\%$ was associated with favorable outcomes to LuPSMA regardless of addition of dual ICI. Genomic profiles could help identify those more likely to benefit from the addition of ICI to LuPSMA, and those with a poor prognosis regardless of treatment.

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Conflicts of Interest Disclosure

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