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Association of prior poly(ADP-ribose) polymerase (PARP) inhibitor therapy with response to 177Lu-PSMA-617 (LuPSMA) in men with DNA damage repair (DDR) mutations.

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Background: LuPSMA, a radioligand therapy targeting the cell surface protein PSMA, is approved for men with PSMA-positive mCRPC previously treated with androgen receptor signaling inhibitor (ARSI) and taxane chemotherapy. Several PARP inhibitors (PARPi) are also currently approved for patients with mCRPC harboring alterations in genes associated with DNA damage repair (DDR). Given that both therapeutics result in DNA damage, we hypothesized that there would be clinical evidence of cross-resistance between the two classes of agents, with decreased efficacy in patients receiving LuPSMA following a PARPi. **Methods:** We abstracted retrospective data from patients at three centers who received at least one cycle of LuPSMA per the FDA label and had panel-based tumor sequencing performed. Patients with PARPi qualifying mutations were included in the analysis. PSA_{50} responses (i.e. ≥50% decline in PSA from baseline), PSA progression free survival (PFS) and overall survival (OS) following treatment with LuPSMA were compared between patients who received prior PARPi (PARPi-T cohort) and those who did not (PARPi-NT cohort). **Results:** Forty-nine patients with a PARPi qualifying alteration who received at least one cycle of LuPSMA were identified. Baseline characteristics (Gleason score, visceral metastases, race, ECOG PS, PSMA $SUV_{mean/max}$) were similar between cohorts. Prior non-PARPi lines of therapy, including receipt of radium-223 (14% vs 21%), carboplatin (33% vs 36%), ≥ 2 prior ARSI (67% vs 68%), and ≥ 2 prior taxanes (43% vs 47%) were also similar between the PARP-NT and PARP-T cohorts respectively. Median PSA PFS and OS were both significantly increased in the PARPi-NT cohort as compared to the PARPi-T cohort (Table). PSA_{50} responses were numerically increased in the PARP-NT cohort, although this did not reach statistical significance. The most common PARPi qualifying alteration was *BRCA2* (N=15). PARP-NT patients with BRCA2 alterations had significantly increased PSA PFS and OS as well as PSA_{50} response rates compared to the PARP-T patients. **Conclusions:** Prior receipt of PARPi therapy appears to negatively associate with the clinical activity of LuPSMA, with the largest difference in outcomes observed in patients with *BRCA2* mutations. These data support the hypothesis that PARPi therapy may lead to clinically significant cross-resistance with LuPSMA. Prospective studies to evaluate the optimal sequence of LuPSMA and PARPi therapy are justified. Research Sponsor: None.

LuPSMA clinical outcomes.

	All PARPi Eligible Patients			Patients with *BRCA2*-mut		
Clinical Outcome	**PARPi-NT**	**PARPi-T**	**p-value**	**PARPi-NT**	**PARPi-T**	**p-value**
PSA50 responses, n/N (%)	13/21 (61%)	13/28 (46%)	0.28	4/4 (100%)	4/11 (36%)	0.029
PSA PFS (Months, 95% CI)	8.2 (6.1 - NR)	4.1 (2.7 - 8.8)	0.024	10 (8.9 - NR)	2.2 (1.6 - NR)	0.051
OS (Months, 95% CI)	23 (NR-NR)	9 (5.3 - NR)	0.029	23 (NR-NR)	3.1 (2.7 - NR)	0.031