TPS5112 Poster Session

VALOR study: A phase II trial of vorinostat to augment response to 177Lutetium-PSMA-617 in the treatment of patients with PSMA-low metastatic castration resistant prostate cancer.

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Background: ^{177}Lu-PSMA-617 (LuPSMA), a prostate specific membrane antigen (PSMA) targeting radioligand therapy, is approved for men with mCRPC. However, responses are only observed in ~50% of patients, with pre-clinical and clinical data indicating that those with high, homogenous PSMA expression experience the greatest benefit. Therefore, therapeutic strategies to increase PSMA expression may improve outcomes to LuPSMA and potentially other PSMA targeting therapeutics. Our group recently showed that epigenetic repression of the *FOLH1* (PSMA gene) promoter was associated with decreased PSMA expression and that treatment with a histone de-acetylase inhibitor (HDACi) consistently resulted in increased PSMA protein expression both in vitro and in vivo. Based on these results, we are conducting a proof-of-concept clinical trial testing whether the HDACi vorinostat can increase PSMA expression in patients and prime them for improved response to subsequent therapy with LuPSMA. **Methods:** This single-arm, single-center, open label pilot trial seeks to enroll 15 patients with PSMA-low mCRPC who are otherwise eligible for LuPSMA. PSMA-low is defined as baseline total tumor PSMA SUVmean <10, a threshold that has been correlated with inferior outcomes with LuPSMA compared to those with higher SUVmean (PSMA-high). patients receive a 28-day treatment cycle of vorinostat (400mg PO daily) followed by repeat ^{68}Ga-PSMA-11 PET. Patients will then proceed to receive subsequent treatment with LuPSMA per investigator's discretion. The primary endpoint is to determine the conversion rate of PSMA-low to PSMA-high expression as determined by ^{68}Ga-PSMA-11 PET. The target enrollment provides 86% power to detect a conversion rate of 33% with vorinostat- a rate believed to be clinically meaningful and would justify a future randomized trial- relative to an assumed null conversion rate of 5% based on a 1-sample test of binomial proportions with 2-sided α=5. Key secondary endpoints include clinical efficacy of LuPSMA (e.g., radiographic and PSA response rates, PFS, OS) following vorinostat and safety and tolerability of the proposed sequential therapy. Patients enrolled on the trial undergo serial blood collection and metastatic tissue (if safe and feasible) at baseline, post-vorinostat treatment, and following progression on LuPSMA. Blood samples will be processed for analysis of circulating tumor cells (CTC) and (ct)DNA. Detailed analyses of these biospecimens will include orthogonal assessments of PSMA expression (including IHC, CTC staining), RNA sequencing, and methylation profiling. These molecular studies will be correlated with the pre/post vorinostat PSMA PET images and clinical outcomes with LuPSMA. Clinical trial information: NCT06145633. Research Sponsor: Novartis.