TPS5115 **Poster Session**

An oral prostate cancer RIPTAC therapeutic in phase 1 for metastatic castrate resistant prostate cancer (mCRPC).

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Background: New therapies are urgently needed to treat prostate cancer, especially for patients progressing on existing drugs that inhibit the activity of the Androgen Receptor (AR) (e.g. Androgen Receptor Pathway Inhibitors (ARPIs)). Metastatic Castration-Resistant Prostate Cancer (mCRPC) is a more aggressive stage of the disease, characterized by increased AR expression and signaling. To address this unmet medical need, we have developed a Regulated Induced Proximity Targeting Chimera (RIPTAC™) Therapeutic HLD-0915. HLD-0915 is a heterobifunctional small molecule that leverages full length AR (FL-AR) expression in tumor cells to form a trimeric complex with an Essential Protein (EP) needed for cell survival. This results in EP loss of function in prostate cancer cells and a selective antitumor effect. HLD-0915 activity requires only the presence of FL-AR and retains activity regardless of whether there are AR or non-AR aberrations that may otherwise serve as drivers of disease. Preclinically, HLD-0915 treatment results in tumor shrinkage and PSA declines following oral dosing in murine models of castration-resistant and ARPI-resistant forms of the disease, while delivering a favorable therapeutic index. The Phase 1 trial in mCRPC will investigate safety and early signs of efficacy in the intended patient population. **Methods:** This first-in-human, multicenter, open label Phase 1/2 study evaluates the safety, tolerability, and clinical activity of HLD-0915 in patients with mCRPC. Phase 1 consists of monotherapy dose levels employing a Bayesian Optimal Interval (BOIN) design with each dose level starting with a minimum of 3 patients per cohort with the primary objectives of defining the maximal tolerated dose and/or recommended dose for expansion and characterizing safety and tolerability of HLD-0915. This study also aims to characterize the PK profile and assess clinical activity by PSA declines and objective response rate per RECIST and will explore ctDNA, tumor cell genetics, and PD biomarkers. Patients with progressive mCRPC who may or may not have received prior novel antiandrogen therapy, a taxane, or PSMA targeted radioligand will be enrolled. Cohort 1 enrollment begins in January 2025. The Phase 2 portion of the study will confirm the RP2D and clinical activity in up to 3 cohorts which will be decided in the future based on emerging data. Clinical trial information: NCT06800313. Research Sponsor: None.