TPS5115

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 an aggressive stage of disease characterized by increased AR expression and signaling. To address this unmet medical need, we 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 by binding AR and an essential protein needed for cell survival, in this case BRD4. This results in BRD4 loss of function in prostate cancer cells and a potent 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 decline 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 investigates safety and early signs of efficacy in the intended patient population.

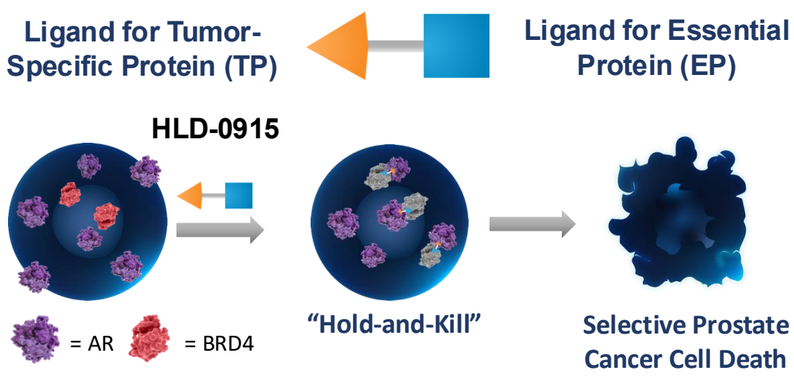
METHODS

This first-in-human, multicenter, open label Phase 1/2 study (NCT06800313) evaluates the safety, tolerability, and clinical activity of orally administered HLD-0915 in patients with mCRPC. Phase 1 consists of monotherapy dose levels employing a Bayesian Optimal Interval (BOIN) design with a minimum of 3 patients per cohort. The primary objectives are to define the maximal tolerated dose and/or recommended dose for expansion and characterize safety and tolerability of HLD-0915. This study also aims to characterize the PK profile and assess clinical activity by PSA decline 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.

The first patient was dosed in February 2025 and in view of preclinical models of mCRPC and human dose predictions, activity may be observed in the first few cohorts of dose escalation. Cohort 1 completed in April with no DLTs and all patients remain on study and continue to receive HLD-0915. Cohort 2 dosing began April 2025, and all 3 patients have received HLD-0915.

FIRST-IN-CLASS AR-BRD4 RIPTAC HLD-0915 for mCRPC

HLD-0915 is a Novel RIPTAC™ Therapeutic

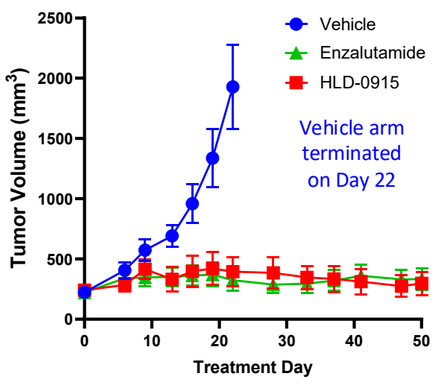


- RIPTACs rely on AR expression; AR does not need to be a driver
- Forms a tumor specific, proapoptotic ternary complex that causes BRD4 loss of function (LoF)
- BRD4 inactivation (cMYC/HEXIM1/TXNIP) closely tracks trimer complex formation in tumors

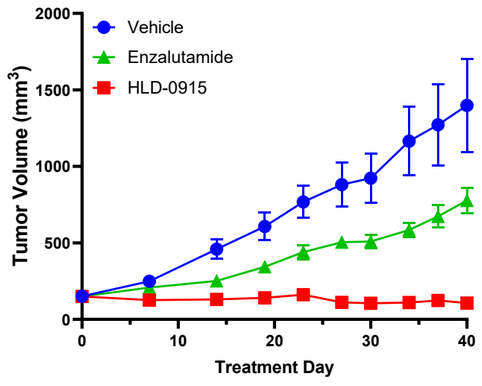
HLD-0915 has a Robust Efficacy Profile Across Multiple Preclinical CRPC Models

Tumor regressions observed in enzalutamide-insensitive models with PSA declines

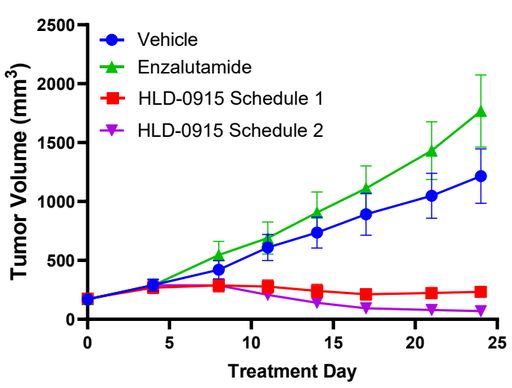
Castrate LNCaP Model
(AR^{T878A}, enzalutamide sensitive)



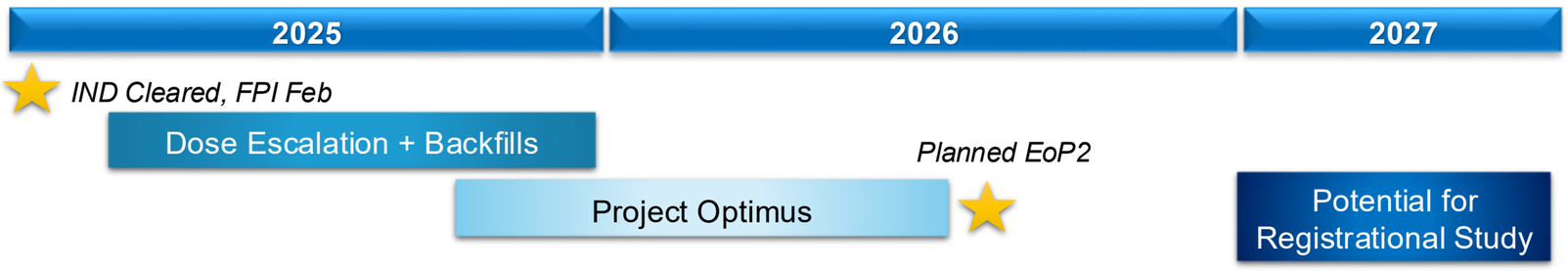
Castrate VCaP Model
(AR^{amp}, V7+, TP53^{R248W}, low enzalutamide sensitivity)



Castrate LNCaP95 Model
(AR^{T878A}, V7+, androgen independent, enzalutamide resistant)



PHASE 1/2 TRIAL DESIGN AND TIMELINES



Dose Escalation (30-35 pts)

Design
- Patients that have progressed on at least one standard of care
- Progressive mCRPC pts with measurable and progressive PSA
- Bayesian optimal design (BOIN); enable flexibility for cohort backfills for biopsy/biomarkers/RECIST

Objectives
- Safety and tolerability of monotherapy
- Evaluate PK/PD and efficacy (i.e. PSA, ctDNA genomics and decreasing tumor fraction, RECIST)

Expansion Cohorts (40-45 pts)

Design
- Evaluate potential responders and confirm optimal dose for development

Objectives
- Assess safety and tolerability
- Confirm RIPTAC MoA and evaluate signs of efficacy (PSA, ctDNA, RECIST)

RIPTACs ARE A POWERFUL MODALITY

RIPTAC is a First-in-Class Anti-Cancer Modality:
- Induced proximity drug with a novel and unique MoA
- Tumor-selective cell death independent of oncogenic driver (ADC-like, but Oral)
- Activity is dependent on TP expression (e.g. AR) and EP LoF (e.g. BRD4) via a stable ternary complex resulting in activity across resistance mechanisms
- Demonstrated preclinical neo-PPI pharmacology for a portfolio of TP:EP pairs across tumor types
- Demonstrated robust *in vivo* efficacy in therapy resistant prostate and breast cancer tumor models

Clinical Development Pathway:
- Prostate: 2025 Phase 1 in mCRPC with AR-RIPTACs
- Breast: IND-enabling underway
- Pipeline development for new tumors types
- Exploring broad platform beyond oncology

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