Phase 1, Dose-Escalation Study of KTX-2001 (an NSD2 Inhibitor) Alone and in Combination with Darolutamide for Metastatic Castration-Resistant Prostate Cancer

Wassim Abida,[1] Ivan de Kouchkovsky,[2] Rahul R. Aggarwal,[2] Joshua M. Lang,[3] Jose De La Cerda,[4] Hannah D. McManus,[5] Andrew J. Armstrong,[5] Neal D. Shore,[6] Alexander Z. Wei,[7] Mark N. Stein,[7] Marijo Bilusic,[8] Geraldine O'Sullivan Coyne,[9] Fuat Bicer,[10] Amir Mortazavi,[10] Elisabeth I. Heath,[11] Miriam Barnett,[12] Erin Flynt,[12] Vinidhra Sridharan,[12] Jason M. Redman,[12] David R. Wise[13]

[1]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York; [2]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA.; [3]University of Wisconsin Carbone Cancer Center.; [4]Urology San Antonio, San Antonio, TX; [5]Department of Medicine, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC.; [6]Carolina Urologic Research Center, Myrtle Beach, SC, USA.; [7]Division of Hematology & Oncology, Columbia University Irving Medical Center, New York, NY; [8]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; [9]START New York City, Long Island, NY; [10]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; [11]Department of Oncology, Mayo Clinic, Rochester, MN; [12]K36 Therapeutics, Boston, MA; [13]Perlmutter Cancer Center, NYU Langone Health, New York, NY

NCT07103018

INTRODUCTION

- **KTX-2001** is an orally bioavailable, small-molecule **NSD2 INHIBITOR** under clinical investigation for the treatment of **METASTATIC CASTRATION-RESISTANT PROSTATE CANCER** (mCRPC).
- **STRIKE-001** is the first-in-human study of KTX-2001 as monotherapy and in combination with darolutamide* for **mCRPC** and is ongoing at U.S. sites.

BACKGROUND

- Androgen receptor pathway inhibitors (ARPI) are first-line therapy for men with metastatic prostate cancer.
- Resistance to ARPIs invariably develops and can occur via lineage plasticity, with a transition to a neuroendocrine-like phenotype (treatment-emergent neuroendocrine prostate cancer [t-NEPC])
- The lysine methyltransferase NSD2 (also known as MMSET/WHSC1) is markedly elevated in prostate cancer cells and is implicated in the development of metastasis, progression to castration-resistance, and the transition to t-NEPC (**FIGURE 1**) in both androgen receptor (AR)-dependent and AR-independent contexts. [1-7]
- Laboratory models of prostate cancer demonstrate that suppression of NSD2 results in a reversal of the adenocarcinoma to neuroendocrine transition and restoration of sensitivity to ARPIs. [3,8]
- KTX-2001 is related to the first-in-class NSD2 inhibitor, gintemetostat (also known as KTX-1001).[9] Gintemetostat has demonstrated a tolerable safety profile and promising single agent activity in patients with heavily pre-treated multiple myeloma.[10]
- We hypothesize that NSD2 inhibition can reverse resistance to ARPIs in patients with progressive mCRPC, including those with neuroendocrine differentiation.

METHODS

STRIKE-001 (NCT07103018) is a multicenter, open-label phase 1 dose escalation trial of KTX-2001 monotherapy (Part A) and KTX-2001 + darolutamide (Part B) in patients with progressive metastatic castration-resistant prostate cancer (**FIGURE 2**).

KEY INCLUSION CRITERIA:

- Metastatic disease documented on conventional imaging (bone metastases on bone scan, or soft tissue metastases on computed tomography or magnetic resonance imaging).
- Willingness to undergo a baseline and on-treatment biopsy of a metastatic site if safe and feasible.
- Progression on or after receiving an ARPI (e.g., abiraterone, enzalutamide, darolutamide, or apalutamide).
- Prior chemotherapy for prostate cancer, unless the participant refused after appropriate medical counseling or is unsuitable for chemotherapy based on investigator's judgement.

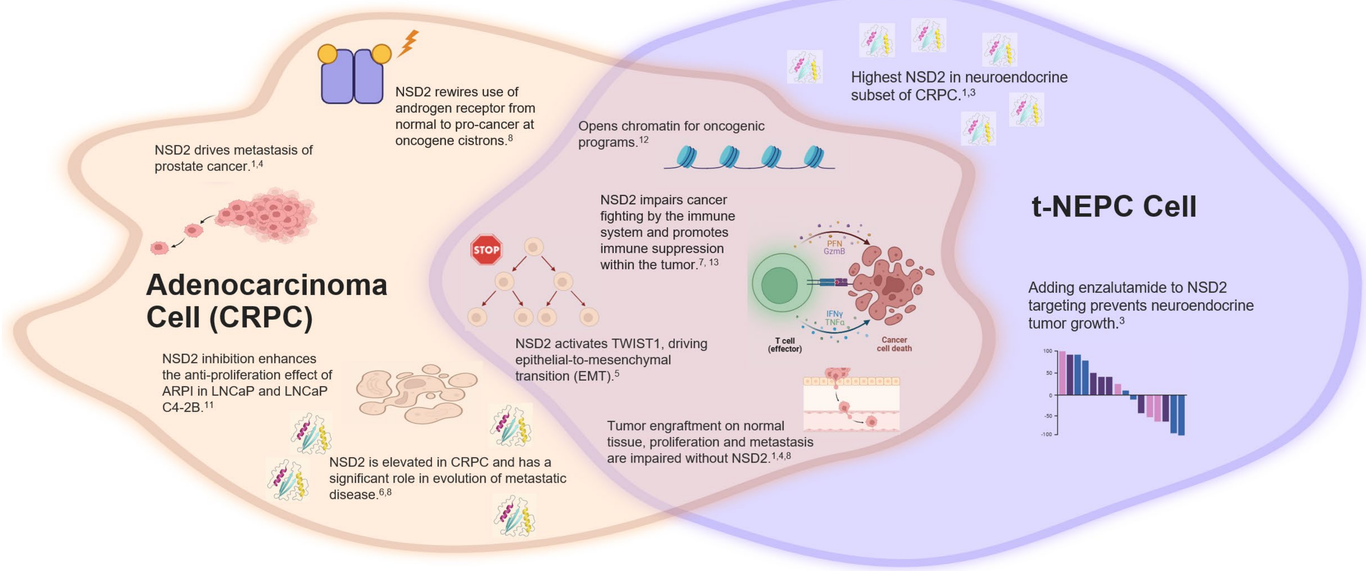
KEY EXCLUSION CRITERIA:

- Pure high-grade neuroendocrine prostate cancer or histopathological diagnosis of pure small-cell carcinoma (unless this diagnosis is meant to refer to features of t-NEPC).

ABBREVIATIONS

AR = Androgen receptor; ARPI = Androgen receptor pathway inhibitors; cfDNA = Cell-free DNA; CTC = Circulating tumor cells; EMT = epithelial-to-mesenchymal transition; mCRPC = Metastatic castration-resistant prostate cancer; MMSET = Multiple myeloma SET domain; MTD = Maximum tolerated dose; NSD2 = Nuclear SET domain–containing 2; RP2D = Recommended phase 2 dose; t-NEPC = Treatment-emergent neuroendocrine prostate cancer; WHSC1 = Wolf–Hirschhorn syndrome candidate 1

FIGURE 1. NSD2 is implicated in progression of prostate cancer, resistance to ARPIs and the transition from adenocarcinoma to treatment-emergent neuroendocrine prostate cancer (t-NEPC). The combination of NSD2 inhibition plus ARPI has been shown to have greater tumor growth suppression than either treatment alone in models of both neuroendocrine prostate cancer and castration-resistant adenocarcinoma. Created with BioRender.com



STUDY DESIGN

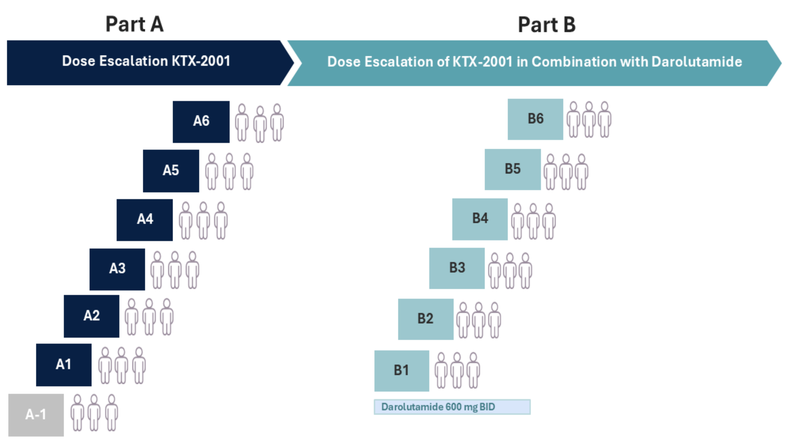


FIGURE 2. KTX-2001 is taken orally as monotherapy (Part A) and in combination with darolutamide (Part B) in 21-day cycles. Dose escalation of KTX-2001 in Parts A and B will follow a 3+3 design and occur in parallel across planned dose levels. Select dose levels will enroll backfill participants for dose optimization.

OBJECTIVES

PRIMARY:

- Investigate the safety and tolerability of KTX-2001 in participants with mCRPC and determine the MTD/highest exposure dose and schedule for KTX-2001 as a single agent.
- Investigate the safety and tolerability of KTX-2001+darolutamide in participants with mCRPC.
- Determine the RP2D of KTX-2001 based on data from Part A and Part B.

SECONDARY:

- Characterize PK parameters of KTX-2001 when administered as single agent or in combination with darolutamide.
- Assess preliminary efficacy of KTX-2001 as monotherapy and KTX-2001 in combination with darolutamide.

EXPLORATORY:

- Evaluate the PK and PD effects of KTX-2001 as a single agent and in combination with darolutamide.
- Evaluate the effect of study treatment on circulating tumor cells (CTCs) and cell free DNA (cfDNA).

REFERENCES

1. Aytes A, et al. *Nat Commun.* 2018;9:5201; **2.** Husmann D, Gozani O. *Nat Struct Mol Biol.* 2019;26(10):880–889; **3.** Li JJ, et al. *Nature.* 2026;649:216–226; **4.** Topchu I, et al. *Cell Mol Life Sci.* 2022;79(6):285; **5.** Ezsponda T, et al. *Oncogene.* 2013;32(23):2882–2890; **6.** Filon M, et al. *Br J Cancer.* 2021;125(2):247–254; **7.** Chava S, et al. *Cell Mol Life Sci.* 2025;82(1):268; **8.** Parolia A, et al. *Nat Genet.* 2024;56:2132–2143; **9.** Lewis CA, Schmidt C, Beebe L, Connolly TJ. *J Biol Chem.* 2025;301(7):110382; **10.** Usmani S, et al. *Blood.* 2025;146(Suppl 1):250; **11.** Internal K36 data; **12.** Ma Z, et al. *J Med Chem.* 2023;66(16):10991–11026; **13.** Li Q, et al. *Sci Rep.* 2023;13(1):21629.

SUMMARY

- KTX-2001 is an oral, small-molecule NSD2 inhibitor being evaluated clinically in mCRPC.
- This ongoing, first-in-human clinical trial is assessing KTX-2001 administered as monotherapy or in combination with darolutamide for the treatment of mCRPC at clinical sites in the U.S.
- Additional details are available at clinicaltrials.gov: NCT07103018.
- For questions or comments, please email jredman@k36tx.com.

*Darolutamide is supplied by Bayer AG for use in this study.