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FTX-6274, an EED Inhibitor, Demonstrates Robust Efficacy in Castration Resistant Prostate Cancer (CRPC)

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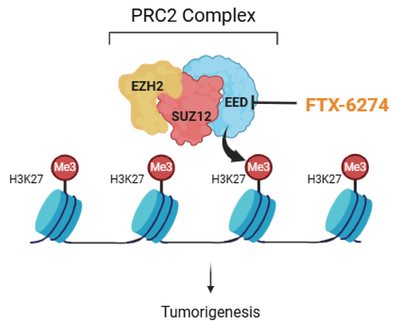
1. Background

Embryonic ectoderm development (EED) is one of the core subunits of the polycomb repressive complex 2 (PRC2) complex which plays important roles in regulating gene expression through its histone H3K27me3 methyltransferase activity.

Dysregulation of PRC2 has been implicated in the development of solid tumors including metastatic prostate cancer and is associated with poor clinical outcomes.



FTX-6274 is an orally bioavailable, highly selective, and potent (0.3 nM Kd) small molecule inhibitor of EED with excellent cross species pharmacokinetics, low efflux liability, and low DDI-risk based on preclinical studies.

2. FTX-6274 treatment causes tumor regression in a Karpas-422 xenograft model

FTX-6274 administered orally twice daily induced tumor regression compared to mevrometostat in the Karpas-422 Diffuse Large B-cell Lymphoma (DLBCL) model. FTX-6274 was well tolerated at the dose assessed.

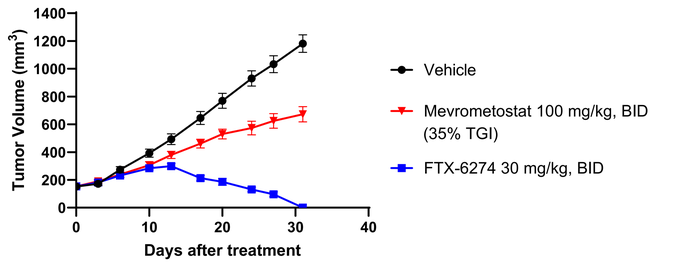
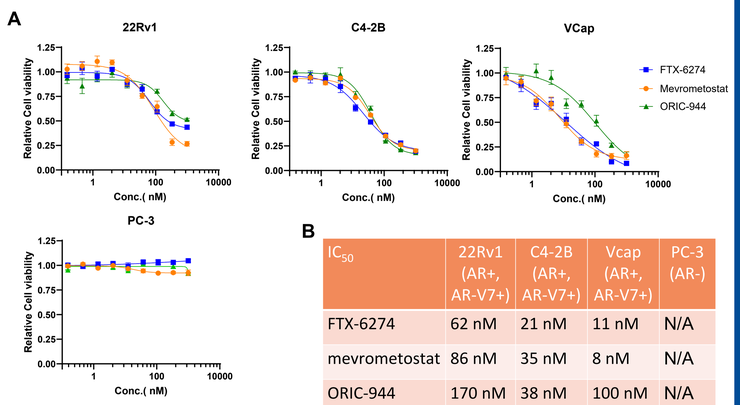


Figure 1: Tumor growth inhibition graph in Karpas-422 DLBCL model; Average tumor volume ± SEM, n=10/group; significant difference in all treatment group vs vehicle.

3. FTX-6274 is potent in multiple AR positive prostate cancer cell lines



B

IC_{50}	22Rv1 (AR+, AR-V7+)	C4-2B (AR+, AR-V7+)	Vcap (AR+, AR-V7+)	PC-3 (AR-)
FTX-6274	62 nM	21 nM	11 nM	N/A
mevrometostat	86 nM	35 nM	8 nM	N/A
ORIC-944	170 nM	38 nM	100 nM	N/A

Figure 2: (A) Prostate cancer cell lines treated with FTX-6274 for 20 days total with serial re-seeding and drug application every 4 days. Cell viability was assessed at indicated time-points against DMSO treated cells using CellTiter-Glo assay. **(B)** Summary of IC_{50} for each cell line

4. FTX-6274 shows robust efficacy in castration sensitive prostate cancer

Oral dosing of FTX-6274 shows strong single agent efficacy in castration sensitive tumor xenografts in intact mice.

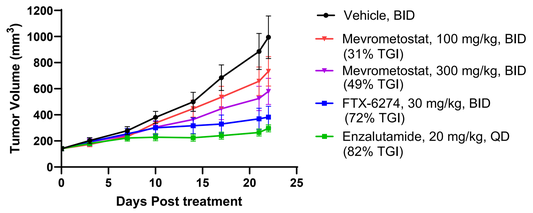
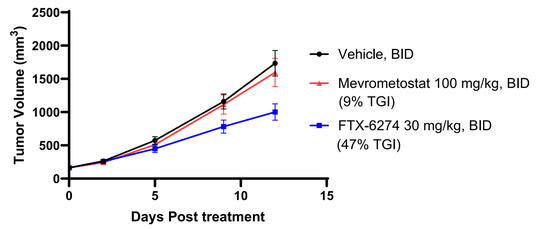


Figure 3: Twice daily oral administration of FTX-6274 in LnCap tumor-bearing mice in intact setting; average tumor volume ± SEM, n=8/group; significant difference in enzalutamide, FTX-6274 and mevrometostat 300 mg/kg treatment group vs. vehicle

5. FTX-6274 has increased survival in enzalutamide resistant model

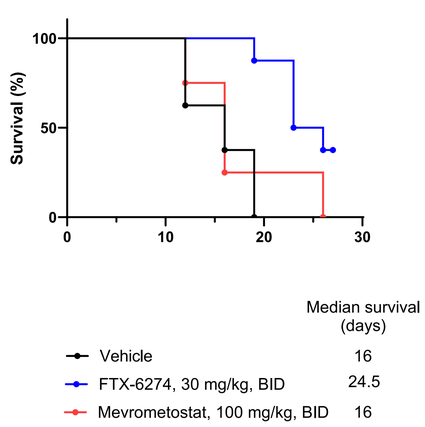
Oral dosing of FTX-6274 in 22Rv1 xenografts in intact setting mice shows strong single agent efficacy and tumor growth inhibition.

A



FTX-6274 prolongs survival in 22Rv1 xenografts in intact mice compared to the vehicle group.

B



	Median survival (days)
Vehicle	16
FTX-6274, 30 mg/kg, BID	24.5
Mevrometostat, 100 mg/kg, BID	16

Figure 4: (A) Twice daily oral administration of FTX-6274 in 22Rv1 tumor-bearing mice; average tumor volume ± SEM, n=8/group; significant difference in FTX-6274 treatment group vs. vehicle. **(B)** Survival curve of 22Rv1 xenograft mice treated for 28 days in intact mice. Progression is defined as tumor volume >2000 mm^3 or death n=8/group.

6. FTX-6274 demonstrates robust efficacy in prostate cancer

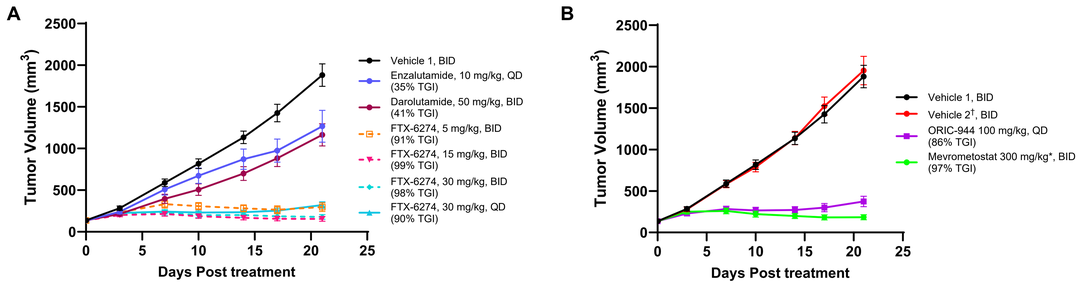


Figure 5: (A) Oral administration of FTX-6274 at doses ranging from 5 to 30 mg/kg QD or BID in C4-2 tumor-bearing mice in intact setting; average tumor volume ± SEM, n=10/ group; significant difference in all treatment group vs vehicle. **(B)** Oral administration of ORIC-944 and mevrometostat in C4-2 tumor-bearing mice; average tumor volume ± SEM, n=10/ group; significant difference in all treatment group vs vehicle. *Mevrometostat was carefully formulated in a wet-mill nanosuspension as per Yamazaki et al, 2020; and formulation integrity confirmed analytically every 7 days. †Vehicle 2 is a mevrometostat specific formulation.

7. FTX-6274 shows strong inhibition of tumor with AR inhibitor in C4-2 Prostate Cancer Xenograft

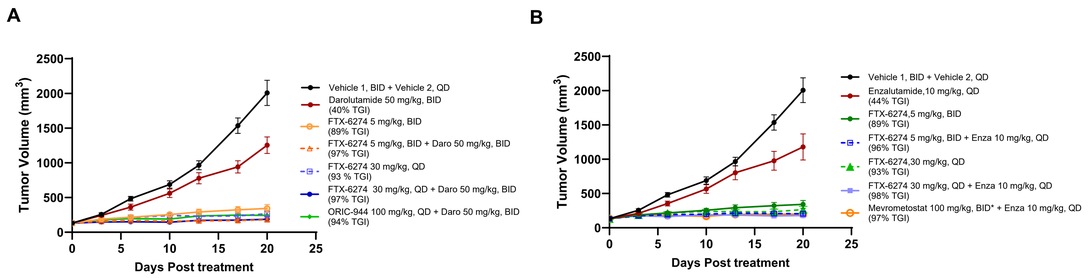


Figure 6: C4-2 tumor xenograft model in intact mice **(A)** Oral administration of FTX-6274 QD or BID in combination with AR inhibitor darolutamide; average tumor volume ± SEM, n=10/group; significant difference in all treatment group vs vehicle. **(B)** Oral administration of FTX-6274 QD or BID in combination with AR inhibitor enzalutamide; average tumor volume ± SEM, n=10/group; significant difference in all treatment group vs. vehicle.

8. FTX-6274 shows strong reduction in H3K27me3 levels in prostate cancer

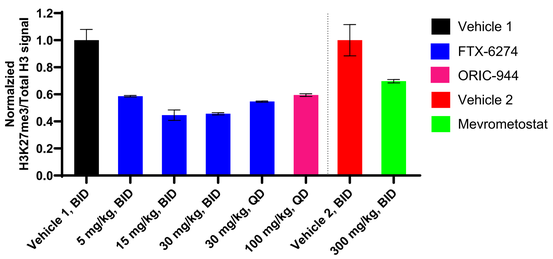


Figure 7: Target engagement in C4-2 xenograft model in intact setting: Tumor samples were collected at day 9 (4h post last dose). Average H3K27 me3/total H3 levels measured by ELISA ± SEM in tumor lysates, n=3/group; significant difference in all doses of FTX-6274 and ORIC-944 treatment group vs vehicle.

9. Summary

FTX-6274 is a small molecule EED inhibitor that shows great potential in treating various cancers. Following initial work in a Karpas-422 DLBCL model that demonstrated full tumor regression, FTX-6274 was explored in prostate cancer. Multiple xenograft studies demonstrate the potential of FTX-6274 to treat castration -resistant and -sensitive prostate cancer, supporting both monotherapy and combinations with ARPIs. In multiple contexts across nonclinical models, FTX-6274 shows similar or superior tumor growth inhibition to either mevrometostat or ORIC-944, and at considerably lower doses.

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Contact Information

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DISCLOSURE: All individuals involved are either current or former full-time employees of Fulcrum Therapeutics Inc. and have or had a financial interest in Fulcrum.