Development of evexomostat / SDX-7320 for the treatment of prostate cancer.

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Background – MetAP2, Prostate Cancer and Metabolism

- Treatment of advanced prostate cancer (PCa) with androgen deprivation therapy and androgen receptor (AR) antagonists (e.g. enzalutamide) provides incremental improvements in survival, but patients inevitably develop resistance highlighting an urgent need for new therapies.
- Continuous AR suppression drives systemic metabolic dysfunction including increased insulin resistance, hyperleptinemia and reduced circulating adiponectin in addition to molecular reprograming in tumours.
- Elevated expression of the enzyme methionine aminopeptidase type2 (MetAP2) has been identified in multiple tumor types[1,2]. Elevated expression of MetAP2 is associated with higher grade tumors and worse outcomes[3].
- MetAP2 inhibitors have clinical activity in oncology[4,5] and in obesity/type 2 diabetes[6,7]. However, clinical development of small molecule MetAP2 inhibitors has been hampered by CNS toxicity[8].
- The novel MetAP2 inhibitor evexomostat/SDX-7320 is now in two phase 2 trials for metastatic breast cancer testing its ability to attenuate intrinsic or drug-induced metabolic dysfunction and to improve clinical outcomes when combined with standard of care treatments.

Hypothesis and Aims

- We hypothesise that evexomostat/SDX-7320, in combination with SoC, will delay treatment resistance in advanced, castration-resistant prostate cancer.
- We tested the utility of evexomostat/SDX-7320 in delaying tumour growth and the progression of disease in androgen-sensitive as well as CRPC models of PCa.

Figure 1. Study Design

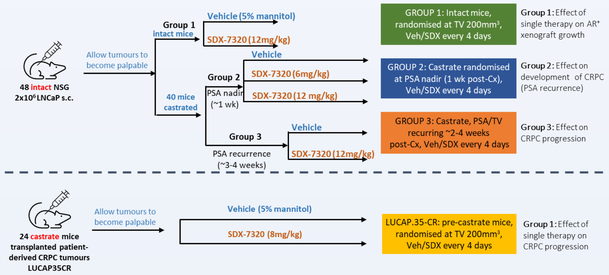

Figure 1: STUDY 1 NSG mice were injected subcutaneously with 2x10^6 LNCaP cells. When tumors reached ~200mm^3, a cohort of intact mice (**Group 1**; n=4/group) received treatment with SDX-7320 (12 mg/kg, s.c., Q4D) or vehicle (5% mannitol/water). The remaining mice were castrated (n=40) and enrolled in treatment arms (12 and 6 mg/kg, s.c., Q4D) upon recovery (**Group 2**; n=14) or after recurrence of tumor growth (12 mg/kg, s.c., Q4D; **Group 3**; n=26). STUDY 2 NSG mice were castrated and 2 weeks later, transplanted with seeds from LUCaP.35CR castrate-resistant patient-derived xenograft[Lam]. When tumors reached ~250mm^3, mice received treatment with SDX-7320 (8 mg/kg, s.c., Q4D) or vehicle (5% mannitol/water). ANALYSIS Tumor growth and body weight were assessed 2x/wk. Serum PSA, 1x/wk. At end point, tumors were weighed and snap frozen for RNAseq analysis or formalin fixed IHC processing. We assessed the effect of SDX-7320 on tumor vasculature using the endothelial marker CD34 (ab81289). **For transcriptome analysis** we performed stranded mRNAseq at 150 bp and 30 M paired reads per sample. Cleaned reads were aligned against a chimeric human + mouse genome using the STAR aligner, followed by read counting with RSEM, differential gene expression analysis and functional gene enrichment using the R packages {edgeR} and {gprofiler2}, respectively.

Figure 2. Structure, MoA of Evexomostat/SDX-7320

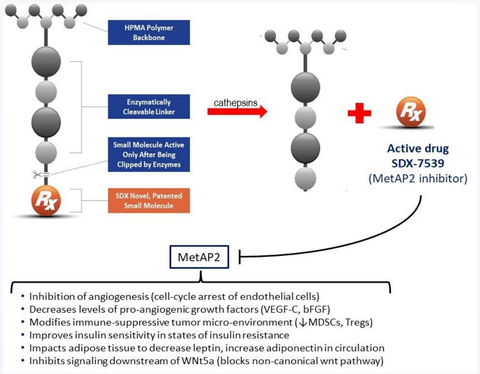

Figure 2: Evexomostat/SDX-7320 is a polymer-drug conjugate of a novel fumagillin-derived MetAP2 inhibitor attached via a cleavable linker to a polymer backbone. This design limits CNS penetration and improves pharmacokinetics relative to small molecule fumagillin-derived MetAP2 inhibitors.

Figure 3. Group 1: Effect of SDX-7320 on AR-Positive Xenograft Growth

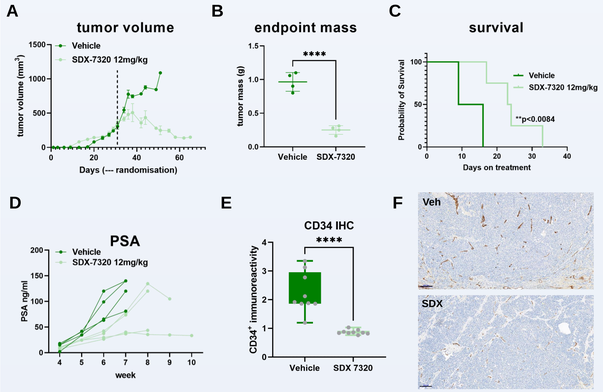

Figure 3: Group 1 were randomised to 12mg/kg SDX or Vehicle when tumors reached >200mm^3 (dotted line). (A) SDX-7320 reversed tumor growth and extended the time to study endpoint, resulting in (B) significantly smaller tumor mass and (C) increased survival time (Veh 12.5 vs SDX 23.5 days). (D) PSA did not reflect reduced tumor mass. (E) MetAP2 inhibition has well-described effects on tumor vasculature and protein translation. Tumors from SDX-treated mice had reduced CD34 immunoreactivity. (F) Representative CD34 staining (bars 200µm).

Figure 4. Group 2 Results: Effect of SDX-7320 on Development of CRPC

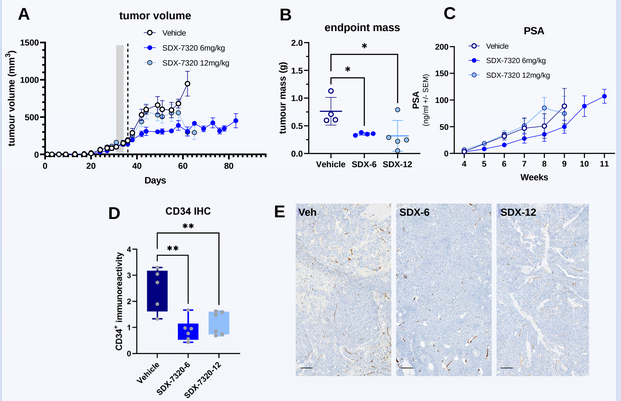

Figure 4: Group 2 were castrated (grey box) to mimic ADT and immediately randomised (dotted line) to 6mg/kg SDX, 12mg/kg SDX or Veh when tumors reached >200mm^3. Both doses of SDX-7320 prevented tumor growth (A), resulting in significantly smaller tumors at study end (B). (C) PSA was not markedly affected by SDX treatment compared to control. (D) Tumors from SDX-treated mice had reduced CD34 immunoreactivity. (E) Representative CD34 staining (bars 200µm).

Figure 5. Group 3 Results: Effect of SDX-7320 on CRPC Progression

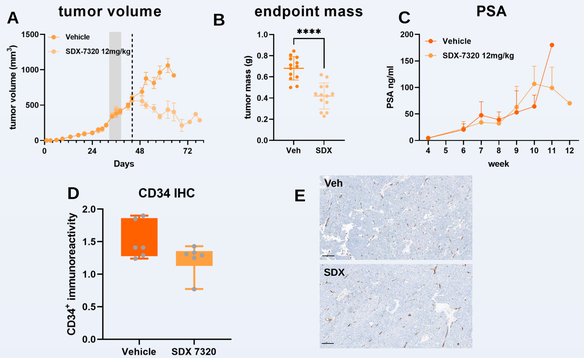

Figure 5: Group 3 were castrated when tumors reached ~200mm^3 (grey box) and randomised when tumor growth recurred (dotted line) to 12mg/kg SDX or Veh. SDX-7320 reversed tumor growth (A), resulting in significantly smaller tumors at study end (B). There was a discordant effect of SDX-7320 on tumor volume and PSA (C). Tumors from SDX-treated mice had reduced CD34 immunoreactivity (D). Representative CD34 staining (E; bars 200µm).

Figure 6. SDX in Patient Derived Xenograft Model: LUCAP35CR

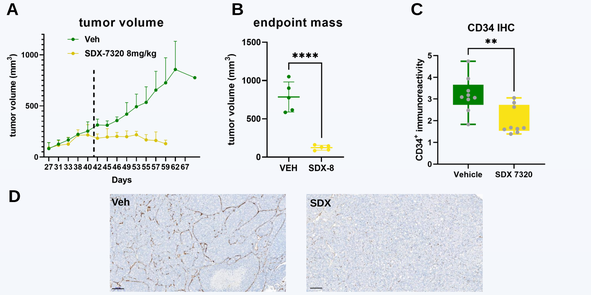

Figure 6: Seeds of patient-derived xenograft LUCaP35.CR were engrafted on the flank of pre-castrated NSG mice. Mice were randomised to 8mg/kg SDX or Veh when tumors reached >200mm^3 (dotted line). SDX-7320 prevented tumor growth (A), resulting in significantly smaller tumors (B). Tumors from SDX-treated mice had reduced CD34 immunoreactivity (C). Representative CD34 staining (D, bars 200µm)

Figure 7. RNAseq and Pathway Analysis

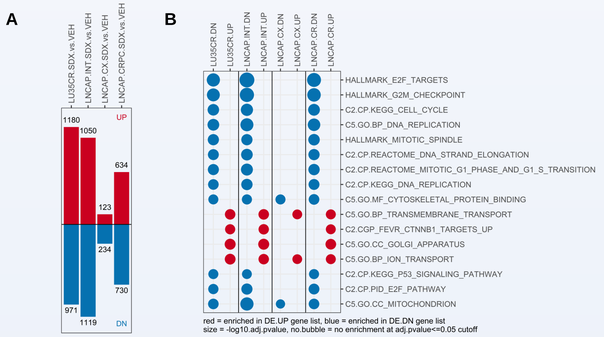

Figure 7: (A) Bar-chart of the number of differentially expressed human genes for each pairwise comparison of treatment groups. Differential gene expression (DE) is defined by abs.FC ≥ 1.5 and FDR pvalue ≤ 0.05. (B) Bubble plot of a selection of significantly enriched (adj.pvalue ≤ 0.05) cellular pathways from the MSigDB (Molecular Signatures Database).

Summary and Conclusions

- Evexomostat/SDX-7320 was profoundly effective in reversing tumor growth in both androgen-sensitive and CRPC models of PCa.
- Clinical exploration of evexomostat/SDX-7320 is warranted in the treatment of CRPC.

References

1) Tucker LA et al, Oncogene. 2008;27(28):3967-3976. doi:10.1038/onc.2008.14. 2).Selvakumar P et al, Clin Cancer Res. 2004;10(8):2771-2775. doi:10.1158/1078-0432.ccr-03-0218. 3) Xie J et al, Cancer Res. 2021;81(9):2510-2521. doi:10.1158/0008-5472.CAN-20-2969. 4) Kudelka AP et al, N Engl J Med. 1998;338(14):991-992. doi:10.1056/NEJM199804023381412 5) Herbst RS et al, J Clin Oncol. 2002;20(22):4440-4447. doi:10.1200/JCO.2002.04.006 6) Hughes TE et al, Obesity (Silver Spring). 2013;21(9):1782-1788. doi:10.1002/oby.20356. 7) Kim DD et al, Diabetes Obes Metab. 2015;17(6):566-572. doi:10.1111/dom.12457. 8) Bhargava P et al, Clin Cancer Res. 1999;5(8):1989-1995.