Development of evexomostat/SDX-7320 for the treatment of tumors whose growth and/or metastatic behavior is accelerated by systemic metabolic dysfunction

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Introduction

Obesity contributes to cancer progression via multiple mechanisms: increased leptin, decreased adiponectin, increased adipose tissue estrogen, elevated insulin (secondary to peripheral insulin resistance), and alteration of the tumor immune microenvironment (TIME) which suppresses host anti-tumor immune responses[7]. As such, "metabo-oncology", the study and treatment of tumors whose growth and metastasis is impacted by systemic metabolic dysfunction, is proving to be a new and significant treatment paradigm of recent interest.

Small molecule inhibitors of methionine aminopeptidase type 2 (MetAP2) have previously demonstrated clinical activity both as anti-tumor agents[6, 2] and against obesity/type 2 diabetes[3, 4]. However, clinical development of some small molecule, fumagillin-based MetAP2 inhibitors has been hampered by hampered by CNS toxicity and/or poor drug-like properties[1, 5 8].

SDX-7320 is a copolymer-drug conjugate of a novel fumagillin-derived MetAP2 inhibitor (SDX-7539) attached via a cleavable amino acid linker to a hydroxypropylmethacrylamide (HPMA) backbone. This design alters biodistribution (limits CNS penetration) to minimize CNS toxicity and improves pharmacokinetics relative to small molecule fumagillin-derived MetAP2 inhibitors such as TNP-470[1, 8].

The in vivo efficacy of SDX-7320 was evaluated alone and in combination with other agents in diet-induced obese (DIO) mice, a syngeneic model of obesity-accelerated breast cancer (using the mouse mammary gland tumor line, EO771) and in a xenograft model of ER+/Her2-/PIK3CA-mutant breast cancer (MCF-7).

SDX-7320 is in two phase 2 trials designed to test its ability to attenuate intrinsic as well as drug-induced metabolic dysfunction and to assess cancer outcomes when combined with standards-of-care in patients with metastatic breast cancer (i.e., NCT05455619, NCT05570253).

Methods

Enzyme assays measuring the release of SDX-7539 from SDX-7320 were carried out at Cyprotex, Inc (Watertown, MA) using cathepsins B, S, L, and K (Sigma, Cat# SRP0289, Enzo Life Sciences, Cat# BML_SE453-0010, Sigma, Cat# SRP0291, Enzo Life Sciences, Cat # BML-SE553-0010, respectively). Enzymes were pre-incubated in 20 mM acetate buffer (pH 5.0 or 7.4) containing 30 mM DTT (Dithiothreitol) and 15 mM EDTA. Reactions were conducted at 37°C. Aliquots taken at various time points were analyzed via LC-MS/MS.

Proliferation of human umbilical vein endothelial cells (HUVECs) was measured at SBH Sciences (Natick, MA) using CellTiter 96® AQueous One Solution (Promega) after incubating cells with test compounds for 72 hours in culture medium containing 2% fetal bovine serum.

At Neosome Life Sciences (Billerica, MA) male C57Bl/6 mice (Taconic) were made obese by feeding a high-fat diet (60 % calories from fat/21% calories from sucrose) for >12 weeks until their average weight was >40 grams. SDX-7320 or vehicle (5% mannitol/water) was dosed subcutaneously (s.c.) every 4 days (Q4D) for 28 days (total of 8 doses). Intraperitoneal glucose tolerance tests (IPGTT) were carried out in the AM (day 24), after 2 hours of food deprivation by injecting dextrose (1 g/kg) into the intraperitoneal cavity at t = 0. Blood samples were obtained via the sub-mandibular gland at the indicated times for measurement of blood glucose. Adipokines as well as insulin were measured in plasma at SBH Sciences (Natick, MA) using commercially available EILSA kits.

Female C57Bl/6 mice (Jackson Lab) were surgically ovariectomized at six weeks of age and, following recovery, were placed on either a high-fat or low-fat diet as described above. Triple-negative cell line EO771 (50,000 cells; from CH3 Biosystems) was injected into the fourth mammary gland and followed until tumors reached approximately 50 mm^3 (measured using a wireless Mitutoyo UWAVE-T digital calipers in conjunction with UWAVE-R) at which time treatment with SDX-7320 was initiated (s.c., Q4D, total of four doses, in 5% mannitol/water). 5-FU was prepared in 0.9% sodium chloride and was administered i.p. at a dose of 10 mg/kg every other day.

Female Nu/nu mice (Jackson Lab) were anesthetized, and each had a 17-β estradiol pellet (0.36 mg, 60-day slow-release pellet) implanted subcutaneously between the scapulae, two days prior to MCF-7 cell implantation. Under anesthesia, 5x10^6 MCF-7 cells in PBS and Matrigel (50/50) were injected into the fourth mammary gland. Following recovery, and after tumors reached an average size of 65 mm^3, dosing with SDX-7320 (S.C, Q4D, in in 5% mannitol/water) and alpelisib (PO, QD, in 0.5% methyl cellulose in water) was initiated.

Immunohistochemistry (IHC) was conducted on formalin-fixed, paraffin-embedded sections at Wax-It Histology Services, Inc (Vancouver, BC) and quantitation of images was conducted using Aperio ImageScope software (v12.4.3.5008, Leica, Inc).

References

1. Bhargava, P. (1999), *Clinical Cancer Research, 5*: 1989–1995.
2. Herbst, RS. (2002), *J. Clin. Oncol*. 20: 4440-7.
3. Hughes, T. (2013), *Obesity, 21*: 1782-1788.
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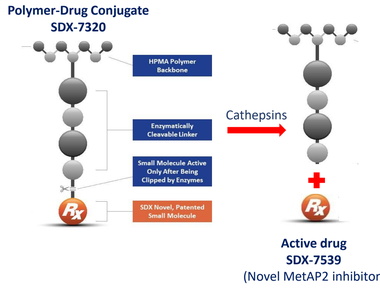
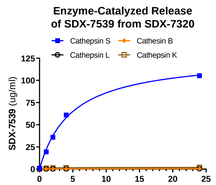
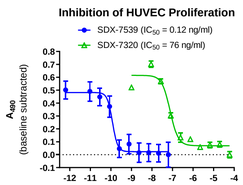
Structure of Evexomostat/SDX-7320

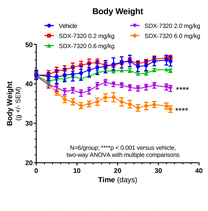


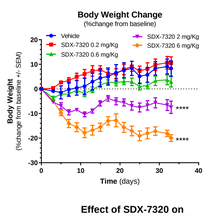
In Vitro Biology

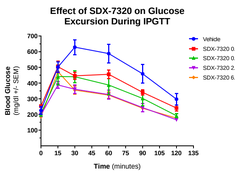


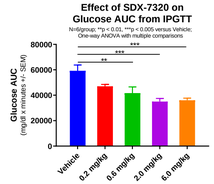


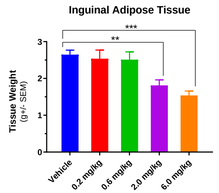
In Vivo Anti-Obesity, Anti-Diabetes Efficacy

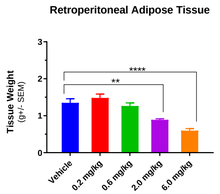




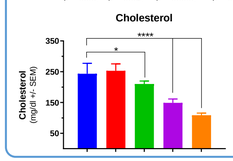


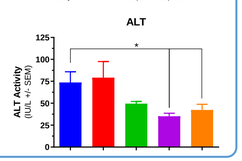




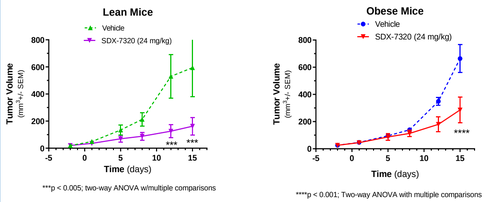


*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001 vs vehicle, one-way ANOVA w/multiple comparisons





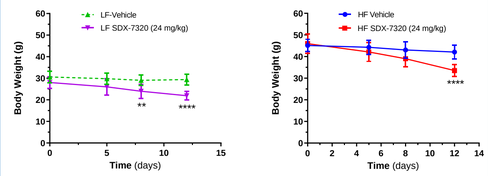
Efficacy of SDX-7320 in Lean and Obese Mice with EO771 TNBC Mammary Gland Tumors



***p < 0.005; two-way ANOVA w/multiple comparisons

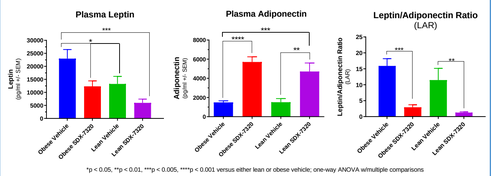
****p < 0.001; Two-way ANOVA with multiple comparisons

Effect of SDX-7320 on Body Weight



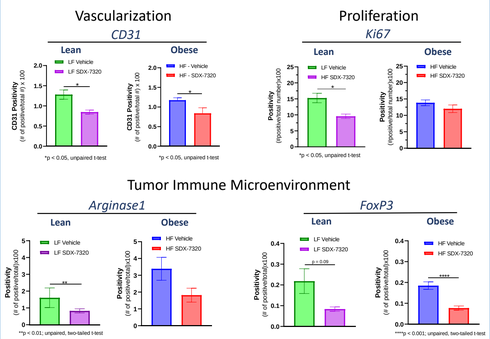
**p < 0.01, ****p < 0.001 versus vehicle; two-way ANOVA w/multiple comparisons

Modulation of Plasma Adipokines by SDX-7320



*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001 versus either lean or obese vehicle; one-way ANOVA w/multiple comparisons

IHC of EO771 Tumors



*p < 0.05, unpaired t-test

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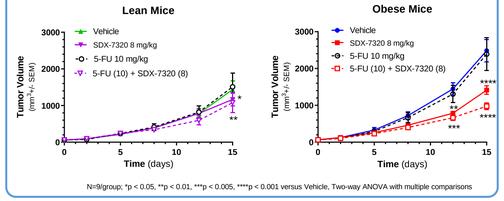
**p < 0.01; unpaired, two-tailed t-test

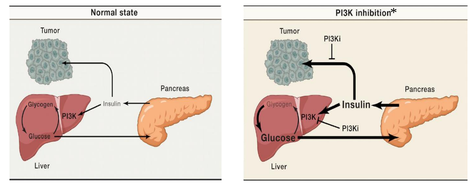
****p < 0.001; unpaired, two-tailed t-test

Efficacy of SDX-7320 +/- 5-FU in Mice with EO771 TNBC Mammary Gland Tumors



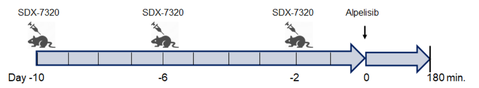
N=9/group; *p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001 versus Vehicle, Two-way ANOVA with multiple comparisons

Hyperglycemia, Hyperinsulinemia Induced by PI3K Inhibitors (e.g., Alpelisib)

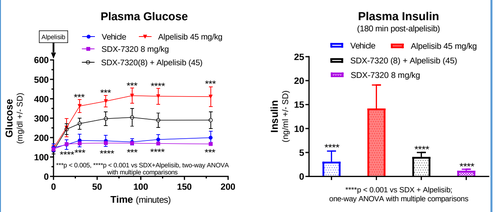


*Inhibition of PI3K in skeletal muscle and adipose tissue after administration of Piqray®/alpelisib also likely contributes to systemic hyperglycemia.

Experimental Design



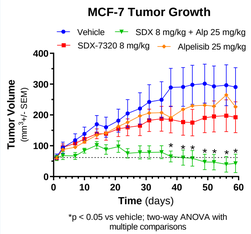
SDX-7320 Controls Acute Hyperglycemia and Hyperinsulinemia Induced by Alpelisib



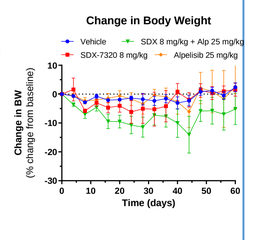
***p < 0.005, ****p < 0.001 vs SDX+Alpelisib, two-way ANOVA with multiple comparisons

****p < 0.001 vs SDX + Alpelisib; one-way ANOVA with multiple comparisons

Efficacy of SDX-7320 +/- Alpelisib in a Model of ER+/Her2-/ PIK3CA-Mutant Breast Cancer



*p < 0.05 vs vehicle; two-way ANOVA with multiple comparisons



Tumor Growth Inhibition (TGI)

%TGI = (1-{Tt/T0 / Ct/C0} / 1-{C0/Ct}) X 100

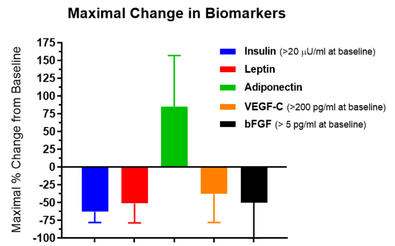
	Vehicle*	SDX-7320 (8 mg/kg)	SDX (8 mg/kg) + BYL (25 mg/kg)	BYL (25 mg/kg)
T_o	64	61	61	61
T_t	293	193	43	226
TGI	0	39	108	23

*One animal in the vehicle group was excluded from TGI calculations due to poor growth (i.e., tumor volume did not exceed 50 mm^3).

Clinical Trials of Evexomostat/SDX-7320

Phase I (completed): SDX-0101 (NCT02743637) "A Dose Escalation Study of SDX-7320 in Patients With Advanced Refractory or Late-Stage Solid Tumors"

- *32 patients enrolled, average prior lines of treatment = 5.8*
- *TEAEs ≥G3 possibly related to study drug were thrombocytopenia (4 patients) and vasculitis (1 patient)*
- *RP2D and schedule is 49 mg/m^2, S.C., Q14D*
- *Decreased insulin, HOMA-IR in patients w/baseline IR*
- *Patients who remained on SDX-7320 >2 months had no new metastatic lesions (n=11)*



Phase 2 Trials

SDX-0102 (NCT05570253): "Phase 2 Randomized Control Trial of Evexomostat (SDX-7320) in Combination with Eribulin for Patients with Metastatic Triple-Negative Breast Cancer and Metabolic Dysfunction: The ARETHA-1 Study"

- *Investigator-initiated trial at MSKCC (N. Iyengar, MD)*
- *Upon safety confirmation, 2:1 randomization will commence for an additional 40 patients*
- *Primary endpoint is change in HOMA-IR score; secondary endpoints are ORR and TEAEs*

SDX-0103 (NCT05455619): "Phase 1b/2 Study of the Safety and Efficacy of Evexomostat Plus Alpelisib and Fulvestrant in Postmenopausal Women at Risk for Hyperglycemia With Advanced Breast Cancer and a PIK3CA Mutation Following Endocrine Therapy and a CDK4/6 Inhibitor: The Amelia-1 Study"

- *Phase 1b/2, open-label, single-arm pilot study to assess the safety of evexomostat plus standard of care treatment alpelisib (PIQRAY®/BYL-719) and fulvestrant (2nd line mBC)*
- *Primary endpoints are the severity and number of hyperglycemic events; secondary endpoints include the anti-tumor benefit of the triplet therapy (6-month ORR, PFS)*

Summary

The novel MetAP2 inhibitor SDX-7320/evexomostat has anti-angiogenic, anti-obesity and insulin-sensitizing properties, with reduced liability for CNS toxicity. SDX-7320 inhibited the growth of obesity-accelerated EO771 tumors. SDX-7320 also attenuated alpelisib-induced metabolic dysfunction, and in MCF-7 xenografts, synergized with alpelisib to inhibit tumor growth.

We are clinically evaluating the hypothesis that addition of SDX-7320 to standards-of-care (SoC) in oncology patients with intrinsic or drug-induced metabolic dysfunction will reduce toxicity of SoC and improve cancer outcomes.

We acknowledge Andy J. Dannenberg, MD, for his valuable input into this presentation.