The Amelia™-1 study: A phase 1b/2 study assessing the safety and efficacy of evexomostat (SDX-7320) plus a PI3K or Akt inhibitor and fulvestrant in patients with advanced HR+/Her2- breast cancer.

Program P3-08-18

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Background

- Breast cancers with alterations in the PI3K pathway (e.g., mutations in PIK3CA, Akt or loss of PTEN) exhibit more aggressive disease and lead to worse outcomes compared to those without such alterations[1].
- PI3K/Akt pathway inhibitors alpelisib[2,3], capivasertib[4], inavolisib[5] can cause on-target hyperglycemia leading to hyperinsulinemia, limiting their effectiveness.
- Restoring insulin sensitivity was shown to improve the efficacy of PI3K inhibitors in preclinical models of breast cancer[6].

Rationale

- Inhibitors of methionine aminopeptidase type 2 (MetAP2) have demonstrated clinical activity in oncology[7, 8] and in metabolic diseases such as obesity and type 2 diabetes[9,10].
- Preclinical data showed that MetAP2 inhibition significantly attenuated both alpelisib- and capivasertib-induced hyperglycemia.
- Combination of alpelisib or capivasertib with a MetAP2 inhibitor enhanced anti-tumor activity relative to either agent alone

Approach

- Evexomostat (SDX-7320) is a novel, clinical-stage MetAP2 inhibitor with anti-angiogenic, anti-metastatic and insulin-sensitizing properties.
  - *Evexomostat (SDX-7320) is a prodrug of a novel fumagillin-derived MetAP2 inhibitor (SDX-7539) attached to a hydroxypropyl-methacrylamide (HPMA) backbone[11].*
  - *Polymer conjugation alters biodistribution of the MetAP2 inhibitor, limiting CNS penetration (to minimize CNS exposure and toxicity) and improving pharmacokinetics relative to small molecule MetAP2 inhibitors such as TNP-470 and CKD-732[11].*
  - *Evexomostat (SDX-7320) exhibits unique anti-tumor, anti-metastatic, anti-obesity, and anti-diabetic activity in preclinical models of cancer, obesity, and insulin resistance.*
- Evexomostat is being tested in this Phase 1b/2 proof-of-concept study to demonstrate improved glucose control and enhanced clinical efficacy.
- Evexomostat was well-tolerated in a phase 1 monotherapy study in late-stage cancer patients while improving insulin resistance in patients with elevated insulin at baseline and reducing key angiogenic markers (VEGF-C, bFGF), while preventing the formation of new metastatic lesions (NCT02743637).

References

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4. Turner et al (2023), *New England Journal of Medicine,* PMID 37256976.
5. Turner et al (2024), *New England Journal of Medicine,* PMID 39476340.
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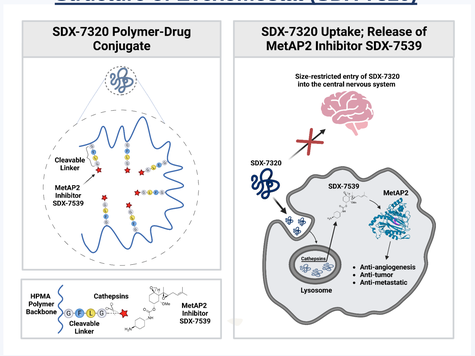
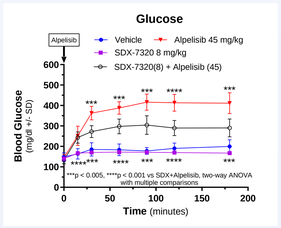
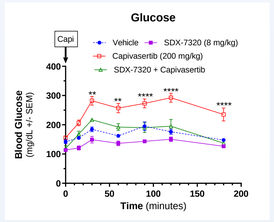
8. Herbst et al (2002), *J. Clin. Oncol*. PMID 12431966.
9. Hughes et al (2013), *Obesity,* PMID 23512440.
10. Kim et al (2015), *Obesity and Metabolism,* PMID 25732625.
11. Cornelius et al (2024), *Molecular Cancer Therapeutics*, PMID 38530115.

Structure of Evexomostat (SDX-7320)

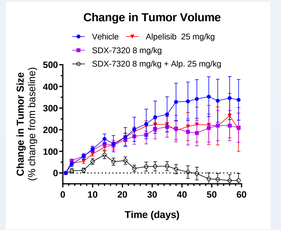


Exevomostat/SDX-7320 Inhibits Alpelisib- and Capivasertib-Induced Hyperglycemia

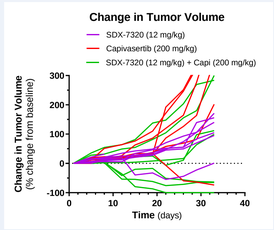




Evexomostat + Alpelisib Synergistically Inhibits Growth of MCF-7 Xenografts



Evexomostat + Capivasertib Inhibits Growth of BT-474 Xenografts



Phase I Trial of Evexomostat (NCT02743637 - completed)

Trial Design

- Patients with advanced cancer; solid tumors only; no CNS tumors
- Sub-cutaneous administration, dose-escalation on a Q7D schedule (28 days/cycle) until >G2 AE, then expand to 3+3
- Dosing schedule changed to Q14D after a DLT @ 49 mg/m^2 Q7D
- Target engagement was measured in whole blood with a custom ELISA
- PK for both SDX-7539 (released active small molecule, validated) as well as SDX-7320 (prodrug/polymer conjugate, exploratory) was assessed in plasma using LC/MS/MS.

Patient Demographics

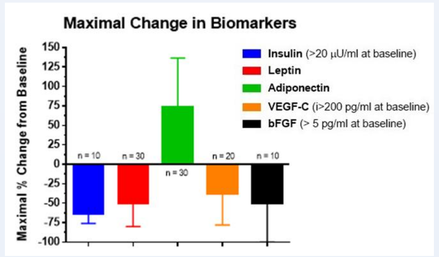
- 32 patients enrolled (14 male, 18 female)
- Mean age: 66 years (49 – 79)
- Mean # prior lines of therapy: 5.8 (1 – 17)
- Cancer types (n): lung (9), colon (6), breast (4), rectal (3), pancreatic (2), appendiceal (2), and one each of carcinoid, cholangiocarcinoma, cervical, endometrial, hepatocellular, urothelial

Safety Summary

- Most common AEs (in >10% of patients; mostly G1/2) were anemia (1 G3), constipation, diarrhea, nausea, vomiting, abdominal pain, decreased appetite, injection site reactions, alopecia and fatigue (1 G3)
- TEAEs ≥G3 possibly related to study drug were thrombocytopenia (4 patients) and vasculitis (1 patient)
- DLT was thrombocytopenia (G3, 4); reversible upon cessation of treatment
- RP2D and schedule is 49 mg/m2, Q14D

Pharmacodynamic Summary

- Best response was stable disease in 21/28 patients (75%); longest duration was 9 cycles (cycle = 28 days); n = 28 patients evaluable for efficacy
- No new metastatic lesions in 89% of patients after 2 Cycles of treatment, and no new metastases for 100% of patients on study >2 Cycles
- Improvements from baseline in key metabolic and angiogenic biomarkers:
  - *Metabolic markers: -63% insulin, -51% leptin, +74% adiponectin*
  - *Cancer markers: -50% bFGF, -38% VEGF-C*



Amelia-1 Clinical Hypothesis:

Pre-treatment with evexomostat prior to initiating alpelisib or capivasertib + fulvestrant in patients with ER+/Her2- mBC with an alteration in their PI3K pathway will reduce the number and severity (grade) of hyperglycemia AEs.

Augmented by evexomostat's anti-tumor and anti-metastatic efficacy, the triplet therapy is expected to result in longer duration of treatment and improved clinical outcomes relative to (alpelisib or capivasertib) plus fulvestrant alone.

Amelia-1 Trial

(NCT05455619; www.amelia1.com)

Primary Endpoint: The safety of evexomostat plus standard of care treatment alpelisib or capivasertib and fulvestrant (combined, the 'triplet therapy'), in terms of the severity and number of hyperglycemic events.

Secondary Endpoints: Objective response rate, clinical benefit rate and 6-month progression-free survival

Exploratory Endpoints: Quality of life, ctDNA, metabolic and oncologic biomarkers (insulin, leptin, adiponectin, bFGF, VEGF-A,-D, -C, apelin, FGF21)

Key Inclusion Criteria:

- Adult ≥18 years or older, no child-bearing ability (post-menopausal or equal)
- Diagnosis of HR+, HER2- breast cancer with a PI3K pathway alteration
- BMI >20 kg/m^2

Dose-Escalation Phase:

- The trial will begin with dose-escalation cohorts of 6 patients each starting at 36 mg/m^2 evexomostat to define the MTD of each triplet therapy.
- A 14-day pre-treatment phase of evexomostat plus fulvestrant is intended to improve insulin sensitivity before initiating the PI3K or Akt inhibitor on C1D15.
- Once the MTD has been defined, additional patients may be enrolled until a total of up to 20 patients have completed at least two cycles of the triplet therapy at that dose to further characterize both safety and efficacy.
- Eight sites are currently open with 13 patients enrolled to date: Miami Cancer Institute, Hoag Memorial Hospital, Vanderbilt University Medical Center, Hope & Healing Cancer Services, Loma Linda University Cancer Center, University of Maryland School of Medicine, Sharp Memorial Hospital.

Treatment	Cycle 1 (28 days)		Cycles 2, 3, 4 etc	
	Day 1	Day 15	Day 1	Day 15
Evexomostat (SDX-7320)	36 mg/m^2, Q4D SC	36 mg/m^2, Q4D SC	36 mg/m^2, Q4D SC	36 mg/m^2, Q4D SC
Fulvestrant	500 mg IM	500 mg IM	500 mg IM	-
Alpelisib	-	300 mg, QD PO	300 mg, QD PO	300 mg, QD PO
Capivasertib	-	400 mg, BID PO (4/7)	400 mg, BID PO	400 mg, BID PO, (4/7)

We acknowledge the support of TD2, Inc (Scottsdale, AZ) and SurvivingBreastCancer.org

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