The Amelia-1 Study: A phase 1b/2a trial of evexomostat (SDX-7320) plus fulvestrant (Faslodex®) and alpelisib (Piqray®) in patients with advanced breast cancer at risk for alpelisib (Piqray)-induced hyperglycemia.

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Background

Breast cancer patients with mutation(s) in the PIK3CA gene have more aggressive disease and worse outcomes relative to patients without PIK3CA mutations[1, 3]. Alpelisib (Piqray®), an inhibitor of PIK3CA, was approved for breast cancer patients with PIK3CA mutations[1]. An on-target toxicity of alpelisib is hyperglycemia leading to hyperinsulinemia which may limit effectiveness of this drug[5]. Patients with baseline insulin resistance, characterized by elevated HbA1c, are at greater risk of developing grade 3,4 hyperglycemia after receiving alpelisib than patients without elevated HbA1c[9]. Restoring insulin sensitivity and reducing systemic insulin levels improved the efficacy of alpelisib in preclinical models of breast cancer[5]. It is logical to consider improvements in insulin sensitivity as a treatment strategy for patients eligible to receive alpelisib (or other PI3Kα inhibitors).

Small molecule inhibitors of methionine aminopeptidase type 2 (MetAP2) have previously demonstrated clinical activity in oncology[2, 4] and in metabolic diseases[6, 8]. However, clinical development of some small molecule, fumagillin-based MetAP2 inhibitors has been hampered by CNS toxicity and/or poor drug-like properties[2, 4, 7].

Evexomostat (SDX-7320) is a clinical-stage MetAP2 inhibitor with anti-angiogenic, anti-metastatic and insulin-sensitizing properties. This new agent is a copolymer-drug conjugate of a novel fumagillin-derived MetAP2 inhibitor (SDX-7539) attached via a cleavable amino acid linker to a hydroxypropyl-methacrylamide (HPMA) backbone. This high molecular weight and highly soluble polymer alters biodistribution (limits CNS penetration) to minimize CNS toxicity and improves pharmacokinetics relative to small molecule fumagillin-derived MetAP2 inhibitors such as TNP-470. Evexomostat exhibits unique anti-obesity, anti-diabetes and anti-tumor activity in preclinical models of obesity, insulin resistance and cancer.

Preclinical combination studies demonstrated that pre-treatment of normal mice with evexomostat significantly attenuated alpelisib-induced hyperglycemia and hyperinsulinemia. In the MCF-7 xenograft model of HR+/Her2-/PIK3CA-mutant breast cancer, low doses of alpelisib synergized with evexomostat in the inhibition of tumor growth.

Evexomostat was well-tolerated in a phase 1 monotherapy safety, dose-escalation study in late-stage cancer patients and improved insulin resistance in patients with elevated insulin at baseline and reduced key angiogenic markers (VEGF-C, bFGF), while preventing the formation of new metastatic lesions (NCT02743637).

References

1. Andre et al (2019), *New England Journal of Medicine,* PMID 31091374.
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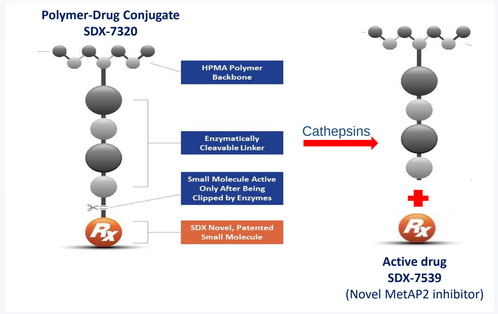
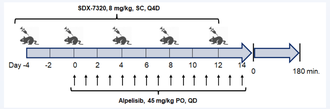
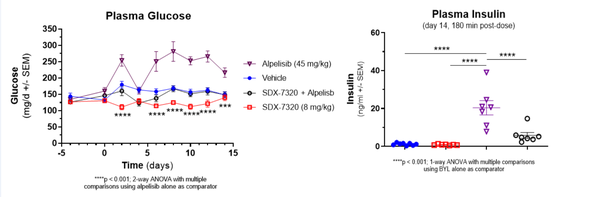
6. Hughes et al (2013), *Obesity,* PMID 23512440.
7. Ingber et al (1990), *Nature*, PMID 1701033.
8. Kim et al (2015), *Obesity and Metabolism,* PMID 25732625.
9. Rugo et al (2020) *Ann Oncol.* 31(8):1001-1010. PMID: 32416251

Structure of Evexomostat/SDX-7320

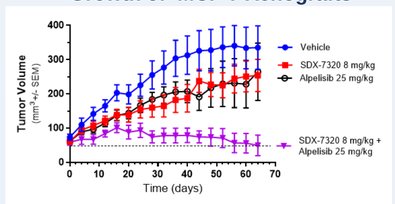


Evexomostat Inhibits Alpelisib-Induced Hyperglycemia, Hyperinsulinemia





Low Doses of Evexomostat + Alpelisib Synergistically Inhibit Growth of MCF-7 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-7320 (pro-drug/polymer conjugate) as well as SDX-7539 (released active small molecule) was assessed in plasma using LC/MS

Patient Demographics

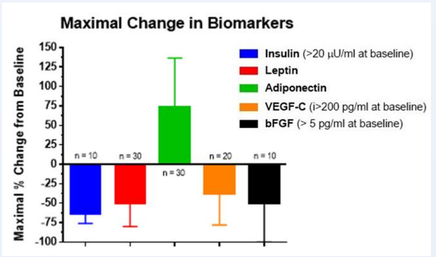
- 32 patients enrolled (14 male, 18 female)
- Mean age: 66 years (49 – 79)
- Mean # prior lines of therapy: 5.8 (1 – 17)
- Cancer types (n): lung (9), colon (6), breast (4), rectal (3), pancreatic (2), appendiceal (2), and one each of carcinoid, cholangiocarcinoma, cervical, endometrial, hepatocellular, 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 is 49 mg/m2, Q14D

PD Summary

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



Amelia-1 Clinical Hypothesis:

Adding evexomostat to the combination of alpelisib + fulvestrant in patients with ER+/Her2- mBC with a PIK3CA mutation will reduce the number and severity (grade) of hyperglycemia AEs.

The addition of evexomostat will lead to fewer discontinuations, dose reductions or dose interruptions due to hyperglycemia and is expected to result in longer PFS relative to alpelisib + fulvestrant.

Amelia-1 Trial

(NCT05455619; www.amelia1.com)

Primary Endpoint: The safety of evexomostat plus standard of care treatment alpelisib (Piqray) and fulvestrant (Faslodex; 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

Key Inclusion Criteria

- Adult ≥18 years or older, no child-bearing ability (post-menopausal or equal)
- Diagnosis of HR+, HER2- breast cancer with a PIK3CA gene mutation
- Patient has baseline metabolic dysfunction defined as fasting plasma glucose <140 mg/dL AND HbA1c ≥5.5% and ≤6.4%
- Prior 1st line CDK 4/6 inhibitor (plus hormone therapy) for >12 months
- BMI >20

Dose-Escalation Phase:

- The trial will begin with dose-escalation cohorts of 6 patients each starting at 36 mg/m^2 in order to define the MTD of the triplet therapy.
- 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.
- The 14-day pre-treatment phase of evexomostat plus fulvestrant starting on Cycle 1, Day 1 (C1D1) before adding alpelisib on C1D15 is intended to improve insulin sensitivity ahead of alpelisib.
- One site is currently open (Toledo Cancer Center, Toledo, OH); no patients enrolled to date

Treatment	Cycle 1 (28-day Cycle		Cycles 2, 3, 4, etc.	
	Day 1	Day 15	Day 1	Day 15
Evexomostat (SDX-7320)	36mg/m^2 SC	36 mg/m^2 SC	36 mg/m^2 SC	36 mg/m^2 SC
Fulvestrant (Faslodex®)	500 mg IM	500 mg IM	500 mg IM	-
Alpelisib (PIQRAY®)	-	300 mg PO	300 mg PO	300 mg PO

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