Synergistic inhibition of MCF-7 mammary gland tumor growth with Piqray®(alpelisib) plus SDX-7320, a novel polymer-conjugated methionine aminopeptidase 2 (MetAP2) inhibitor.

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Introduction

Mutations in the phosphatidylinositol 3-kinase (PI3K) pathway have been observed in about 40% of ER+/Her2- breast cancer patients. Mutation of the catalytic p110α subunit of PI3K activates the pathway within tumors, and increases transmission of intracellular growth signals (Goncalves, 2018). A selective inhibitor of PI3K p110α, Piqray®/alpelisib, was recently approved by the FDA for the treatment of ER+/Her2- breast cancers with mutation(s) in the p110a subunit of PI3K, based on results of the SOLAR-1 trial (Andre, 2019). However, Grade 3/4 hyperglycemia (an on-target toxicity) was seen in >35% of patients, contributing to dose interruptions and dose reductions (Andre, 2019).

Fumagillin is a fungal-derived natural product with anti-angiogenic and anti-tumor activity (Ingber, 1990). A fumagillin-derived small molecule MetAP2 inhibitor (TNP-470) has shown clinical anti-tumor activity (Bhargava, 1999; Herbst, 2002) and two related compounds showed efficacy in treating obesity/type 2 diabetes (Hughes, 2013; Kim, 2015). SDX-7320 is a polymer-drug conjugate of a novel MetAP2 inhibitor (SDX-7539) attached via a cleavable linker to a hydroxypropyl-methacrylamide (HPMA) backbone. This is intended to alter biodistribution (limit CNS penetration) and improve pharmacokinetics relative to small molecule, fumagillin-derived MetAP2 inhibitors. SDX-7320 completed a phase I trial in late-stage cancer patients (NCT02743637) without attributable CNS-related toxicities.

SDX-7320 is being developed to treat cancers whose growth is affected by metabolic hormones such as insulin, leptin and adiponectin (termed “metabo-oncology”). In addition, the known insulin-sensitizing properties of small-molecule MetAP2 inhibitors (Hughes, 2013) as well as SDX-7320 (not shown), suggested that SDX-7320 might combine well with p110a-selective PI3K inhibitors to attenuate on-target hyperglycemia and hyperinsulinemia. Furthermore, interventions that improve insulin sensitivity, when combined with PI3Kα inhibitors in models of breast and pancreatic cancer showed striking anti-tumor efficacy relative to each treatment alone (Hopkins, 2018).

The objective of this study was to evaluate the anti-tumor efficacy of Piqray® and SDX-7320 both alone and in combination in a model of PI3K-mutated, ER+ breast cancer (MCF-7). In addition, the ability of SDX-7320 to prevent the metabolic effects of Piqray® was evaluated in normal, non-tumor bearing mice.

Materials & Methods

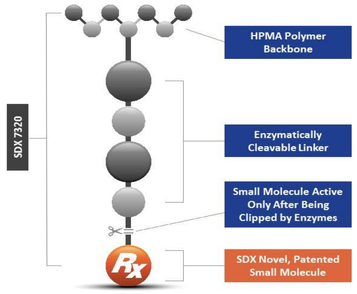
Male C57Bl/6 mice were pre-dosed with SDX-7320 (8 mg/kg) for the indicated times (Q4D, s.c.), after which all mice (except-vehicle treated) received a single oral dose of alpelisib (45 mg/kg, p.o.). Blood glucose was measured via tail vein at regular intervals using a glucometer. Insulin was measured by ELISA from a terminal plasma sample obtained 180 minutes post-alpelisib.

Female nude mice had estrogen pellets surgically implanted and after two weeks of recovery, MCF-7 cells were injected into the fourth mammary gland. When tumors became palpable (i.e., > 50 mm^3) treatment with SDX-7320 (dosed subcutaneously Q4D at 8 or 16 mg/kg) and/or Piqray®/alpelisib (dosed PO, QD at 25 or 45 mg/kg) commenced. Combinations included SDX-7320 at 8 mg/kg plus Piqray®/alpelisib at 25 mg/kg as well as SDX-7320 at 8 mg/kg plus Piqray®/alpelisib at 45 mg/kg. Endpoints included tumor volume and body weight. One-way ANOVA with multiple comparisons was conducted to determine significance of differences in final tumor volume on day 64 relative to vehicle.

References

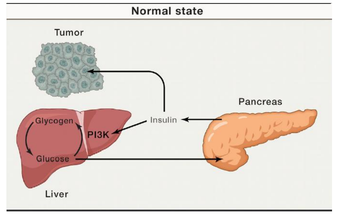
Andre et al (2019), *New England Journal of Medicine,* PMID 31091374.
Bhargava et al (1999), *Clinical Cancer Research,* PMID 10473076.
Goncalves et al (2018), *New England Journal of Medicine,* PMID 30462943.
Herbst et al (2002), *J. Clin. Oncol.* PMID 12431966.
Hopkins et al. (2018), *Nature*, PMID 30051890.
Hughes et al (2013), *Obesity,* PMID 23512440.
Ingber et al (1990), *Nature*, PMID 1701033.
Kim et al (2015), *Obesity and Metabolism,* PMID 25732625.

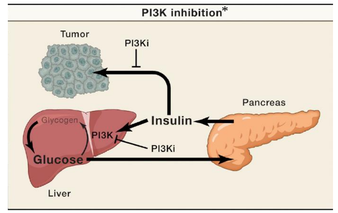
Structure of SDX-7320



Hyperglycemia, Hyperinsulinemia Induced by PI3K Inhibitors

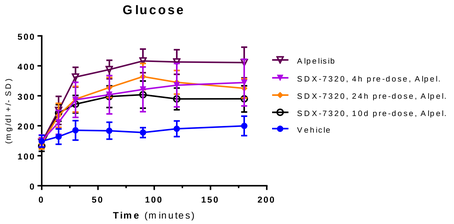
Fruman et al, (2017) *Cell*, 170: 605-635.





*Note that in addition to liver, inhibition of PI3K (and thus insulin signaling) in skeletal muscle and adipose tissue after administration of Piqray®/alpelisib also contributes to systemic hyperglycemia.

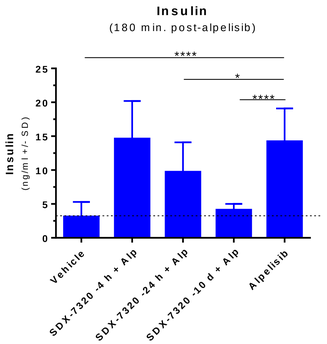
SDX-7320 Attenuates Hyperglycemia Induced by Piqray/alpelisib



	0	15	30	60	90	120	180
7320 4 h Pre	NS	NS	p < 0.01	p < 0.005	p < 0.001	p < 0.01	p < 0.01
7320 24 h Pre	NS	NS	p < 0.01	p < 0.05	NS	p < 0.01	p < 0.005
7320 10 d Pre	NS	NS	p < 0.005	p < 0.005	p < 0.001	p < 0.001	p < 0.001

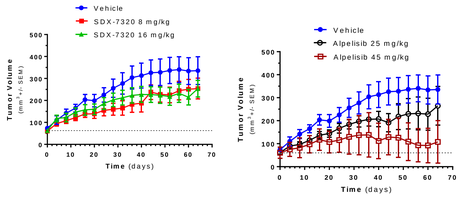
Two-way ANOVA with multiple comparisons, versus alpelisib alone

SDX-7320 Attenuates Hyperinsulinemia Induced by Piqray/alpelisib

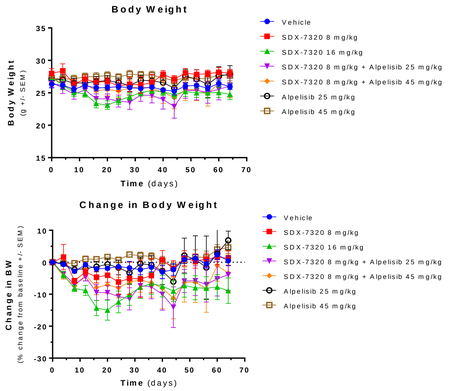


One-way ANOVA with multiple comparisons, versus alpelisib

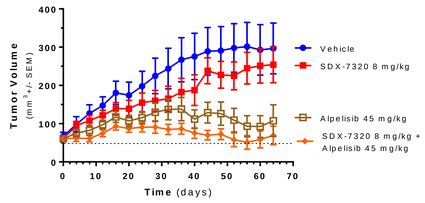
Effect of Single Agents on Growth of MCF-7 Xenografts



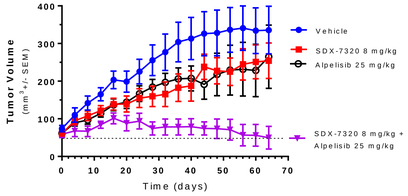
Effect of Single Agents on Body Weight

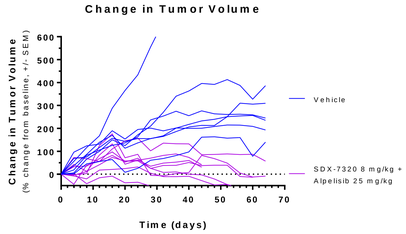


Additive Effect of Higher-Dose Alpelisib + SDX-7320 on Growth of MCF-7 Xenografts



Low Doses of SDX-7320 + Alpelisib Synergistically Inhibited MCF-7 Xenografts





Tumor Growth Inhibition (TGI)

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

Group:	SDX-7320 (8 mg/kg)	SDX-7320 (16 mg/kg)	Alpelisib (25 mg/kg)	Alpelisib (45 mg/kg)	SDX (8) + Alp. (25)	SDX (8) + Alp. (45)
TGI (%)	7.5	11	4.3	77	104	96

Summary and Conclusions

- **Pre-treatment with the MetAP2 inhibitor SDX-7320 significantly attenuated acute hyperglycemia and prevented hyperinsulinemia induced by Piqray®/alpelisib in normal C57Bl/6 mice.**
- **Neither SDX-7320 (8 mg/kg, Q4D) nor Piqray®/alpelisib (25 mg/kg PO, QD) had a significant effect on the growth of orthotopic MCF-7 tumors. However, when combined, a synergistic inhibition of tumor growth was observed.**
- **A Phase 1b/2a clinical trial combining SDX-7320 with Piqray®/alpelisib plus fulvestrant in metastatic breast cancer patients harboring a mutation in PIK3CA is scheduled to begin in 1H 2020.**

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