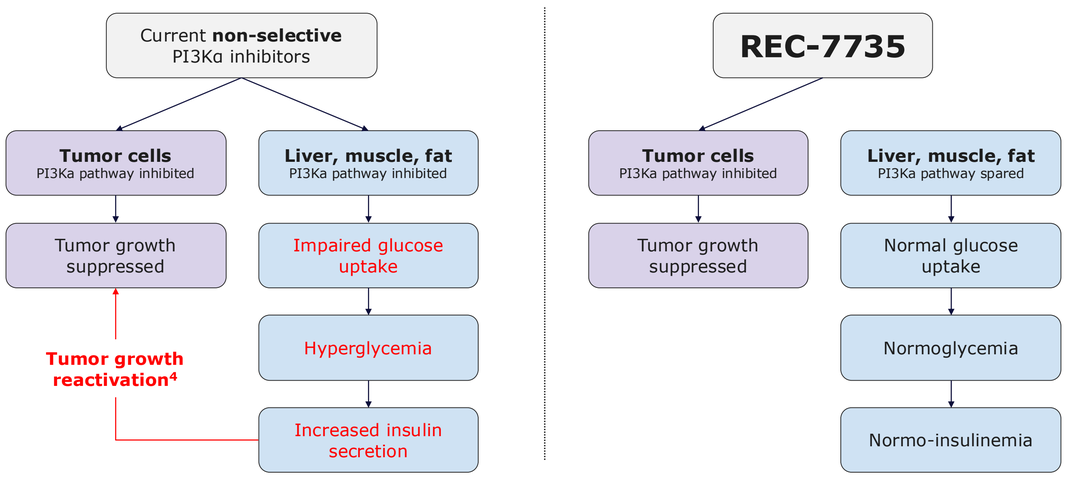
REC-7735: A potent, mutant-selective PI3Kα H1047R inhibitor with preclinical efficacy across multiple solid tumors and no hyperglycemia or other metabolic liabilities

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ABSTRACT #192

1 BACKGROUND

Mutant-selective inhibition of PI3Kα H1047R provides greater target coverage without on-target toxicity



- PI3Kα drives cell proliferation, growth & survival, and has key functions in glucose metabolism and insulin signaling.
- *PIK3CA* is the most frequently mutated oncogene – found in approximately 13% of human cancers[1], with H1047R accounting for ~1/3 of *PIK3CA* mutations.
- Current approved PI3Kα inhibitors do not distinguish mutant from wild-type PI3Kα. Inhibiting wild-type PI3Kα in healthy tissue causes severe toxicities, such as hyperglycemia[2], that force frequent dose reductions and interruptions and limit efficacy.
- Selectively inhibiting PI3Kα H1047R, the most common mutation[3], has the potential to achieve greater, more sustained target coverage while sparing inhibition of wild-type PI3Kα, thus improving efficacy without on-target toxicity.

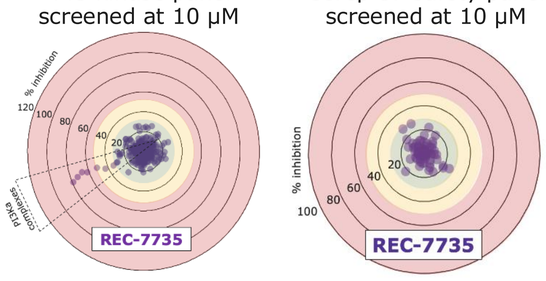
2 RESULTS

REC-7735 is a potent and highly selective inhibitor of PI3Kα H1047R

A **REC-7735 is >100x selective for PI3Kα H1047R**

	T-47D pAKT IC50	Selectivity (WT/H1047R)
Alpelisib	177 nM	1x
Tersolisib	78 nM	6x
REC-7735	**55 nM**	**>100x**

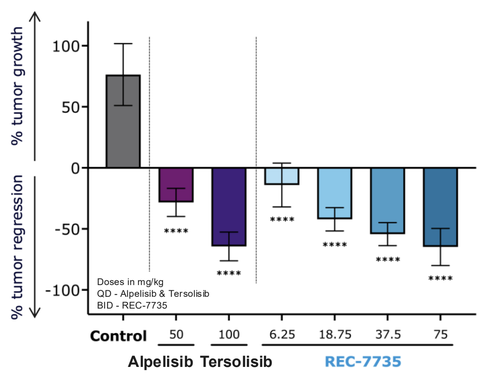
B **No off-targets identified in a 448-kinase panel and Cerep 87 safety panel**



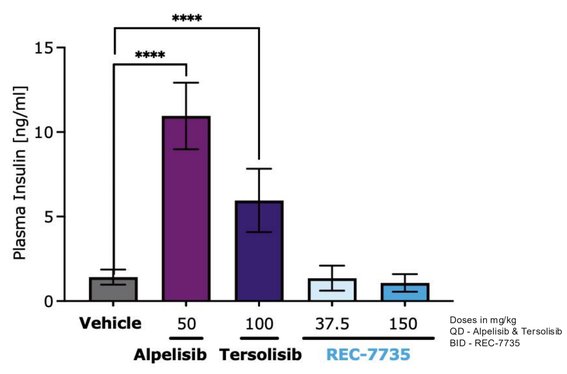
A) REC-7735 is more than 100-fold selective for PI3Kα H1047R (T-47D) over PI3Kα wild-type (SK-BR-3) in cellular pAKT (HTRF) assays.
B) REC-7735 shows no off-targets (>30% inhibition) in both a panel of 448 kinases (Eurofins, KinaseProfiler LeadHunter) and 87 safety-relevant targets (Eurofins, Cerep 87).

REC-7735 displays potent *in vivo* activity with no impact on hyperglycemia markers

A **Dose-dependent tumor regression in HR+ HER2- breast cancer model**

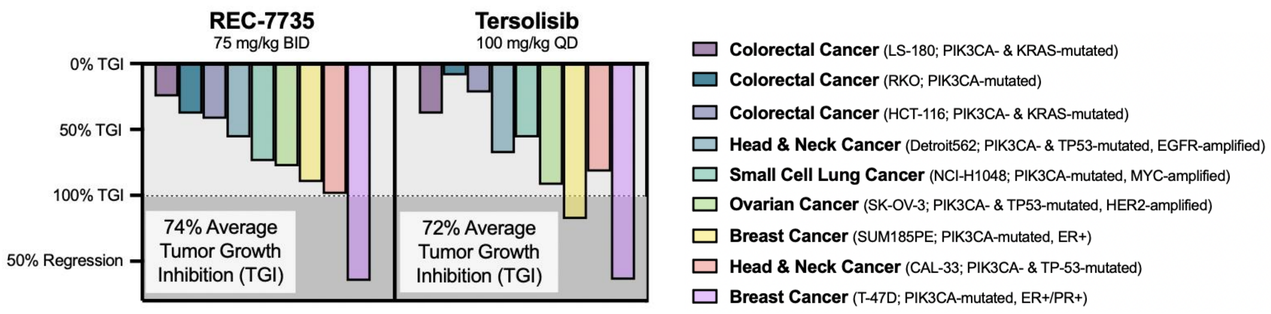


B **No increase in hyperglycemia markers**



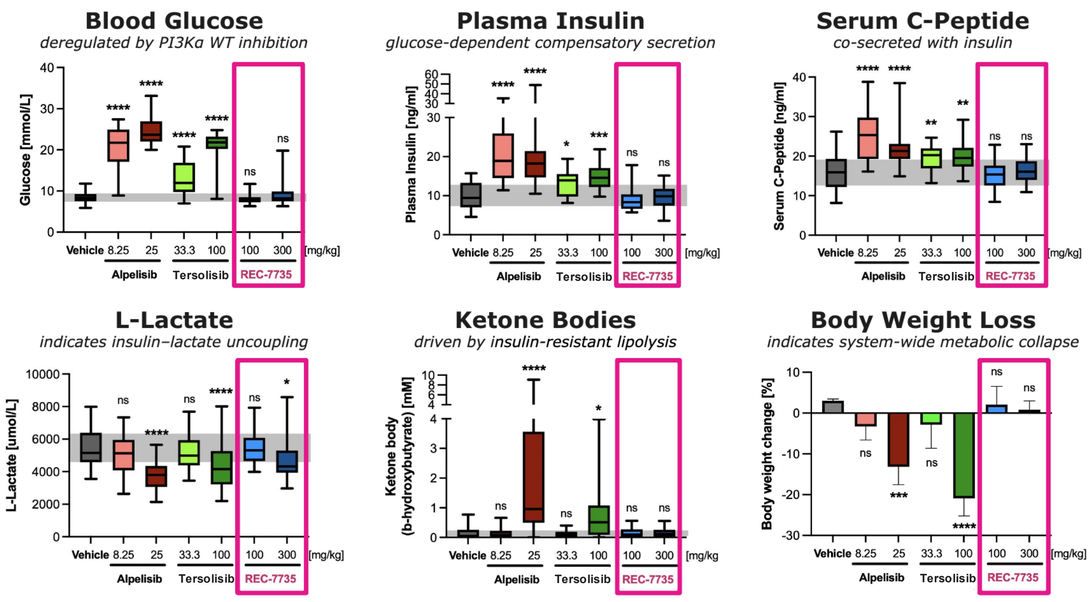
A) *In vivo* T-47D CDX model. n=10 mice per group. Data shown at termination after 14 days of dosing. Measured PK and target engagement (tumor pAKT) was in line with observed tumor regression. **B)** *In vivo* non-tumor bearing mice. n=6 mice per group. Data represents plasma insulin after 5 days of dosing. Plasma glucose and serum C-peptide showed similar trends.
One-way ANOVA with Dunnett's multiple comparisons test versus vehicle. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001; ns, not significant. Data are mean ± SEM.

REC-7735 displays potent *in vivo* efficacy across tumor types



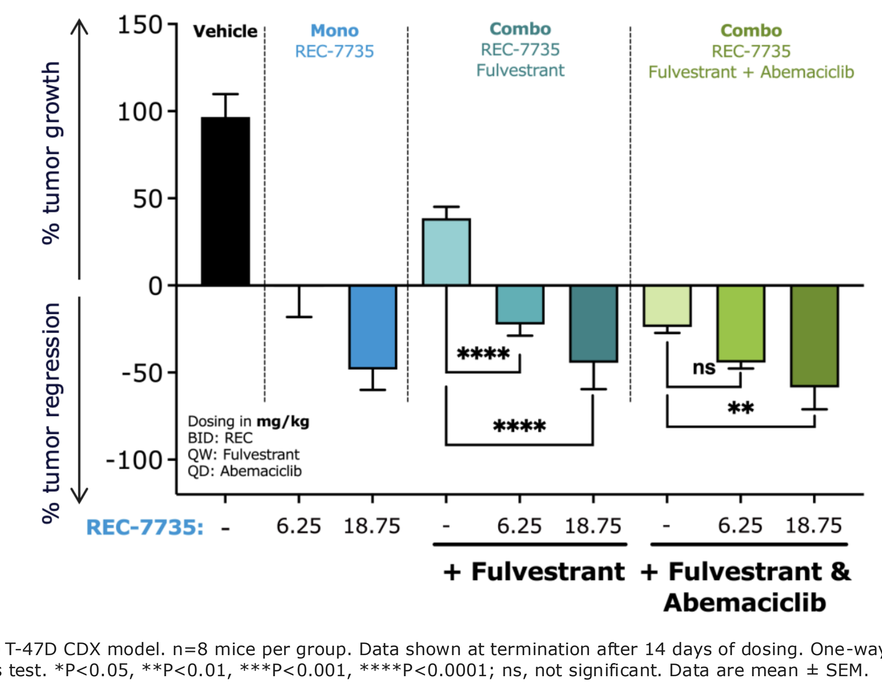
Tumor growth inhibition at termination (14-28 days) across 9 CDX models as indicated.

REC-7735 avoids hyperglycemia and metabolic liability at efficacious exposure in obese T2D ZDF rats[5]



In vivo ZDF rats. n=3 per group. Graphs for Glucose, Insulin, C-peptide, L-Lactate and Ketone Bodies show average values of all 3 animals per group, and all 12 data points over 3 days of treatment. Body Weight Loss graph shows body weight change between baseline and final measurement (5 days). PK and PK/PD analyses indicate compounds were compared at clinically relevant, biologically matched exposures alpelisib: 8.25 mg/kg sub-efficacious dose, 25 mg/kg approaching efficacious dose; STX-478: 33.3 mg/kg efficacious dose, 100 mg/kg supra efficacious dose; REC-7735: 100 mg/kg efficacious dose, 300 mg/kg supra efficacious dose.
One-way ANOVA with Dunnett's multiple comparisons test versus vehicle. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001; ns, not significant. Box plot data show median, IQR, min–max. Bar graphs show mean ± SEM. Gray area indicates vehicle-treated IQR.

REC-7735 outperforms & synergizes with SoC fulvestrant (SERD) ± abemaciclib (CDK4/6i) combo



In vivo T-47D CDX model. n=8 mice per group. Data shown at termination after 14 days of dosing. One-way ANOVA with Tukey's test. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001; ns, not significant. Data are mean ± SEM.

3 CONCLUSION

- REC-7735 is >100x selective for PI3Kα H1047R over PI3Kα wild-type and potently blocks PI3Kα signaling *in vitro* and *in vivo.*
- REC-7735 shows single-agent activity across cancer types - superior to alpelisib and comparable to tersolisib - with no hyperglycemia, hyperinsulinemia, ketosis or weight loss at efficacious doses, even in obese, diabetic animal models.
- REC-7735 has the potential to extend study of PI3Kα-targeted therapy to cancer patients with diabetes, who are not eligible for current PI3Kα inhibitors due to the hyperglycemia risk.
- REC-7735 could provide a wider therapeutic window, which may enable deeper, more sustained PI3Kα inhibition, supporting further study in cancers beyond HR+/HER2- breast cancer and to H1047R-driven non-oncology indications.
- REC-7735 preclinically outperforms & synergizes with the standard-of-care combo SERD ± CDK4/6i.
- REC-7735 is being evaluated in the ZINNIA Phase 1/2 clinical trial for the treatment of PIK3CA H1047R-mutated solid tumors (NCT07819136).

ZINNIA

View poster online

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2) *André F et al. N Engl J Med. 2019;380(20):1929-1940*
3) *Tate JG et al. Nucleic Acids Res 2019;47(D1):D941-D947*
4) *Hopkins BD et al. Nature 2018;560(7719):499-503*
5) *Peterson RG et al. ILAR News 1990;32(3):16-19*