Translate insights ➔ proof points ➔ new medicines

REC-7735

REC-7735: PI3Kα H1047R mutant selective inhibitor designed to improve therapeutic index

Unmet need

- **>21,000**[1] patients with H1047R-mutant solid tumors
- **Current PI3Kα inhibitors are constrained** by:
  - Hyperglycemia and metabolic toxicity
  - Dose interruptions and reductions
  - Limited treatment duration

Thesis & differentiation based on preclinical data

- **>100x mutant selectivity** vs WT PI3Kα, minimizing risk for AEs
- Potential for **superior efficacy and synergistic effect in combination** with SOC
- **Limited to no impact on hyperglycemia markers**

Recursion approach

- AI-powered precision design to **optimize selectivity** and **limit** metabolic liabilities such as **hyperglycemia**
- **242 novel compounds synthesized** from first novel hit to REC-7735

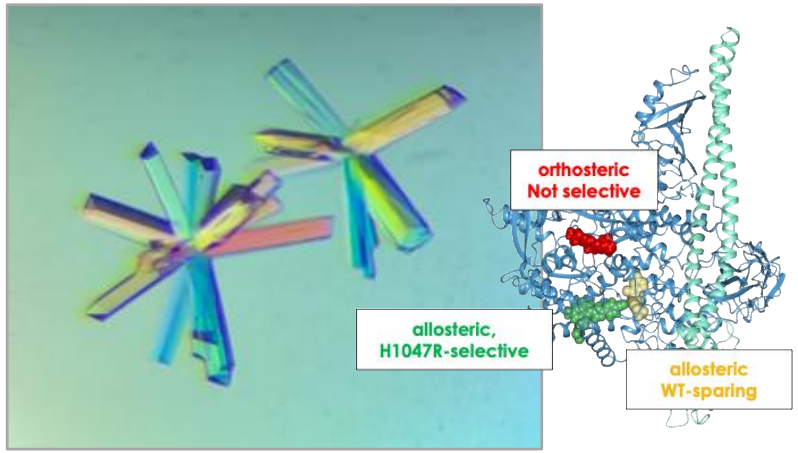
Program Status

- IND enabling studies ongoing
- Go/no-go decision **2H26**

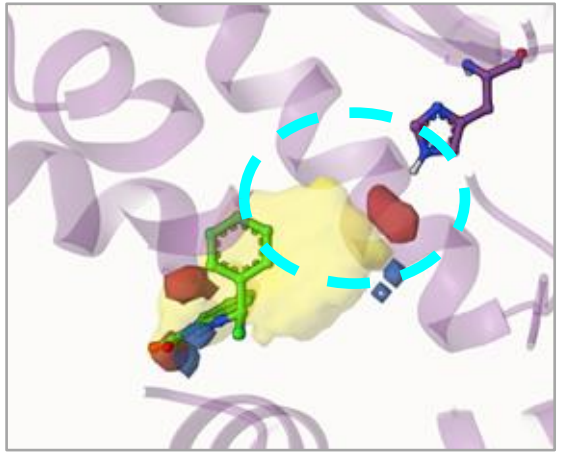
1. Addressable patient populations estimate based on annual US+EU5 and currently identified indications

AI-enabled structure-guided design in a novel binding pocket

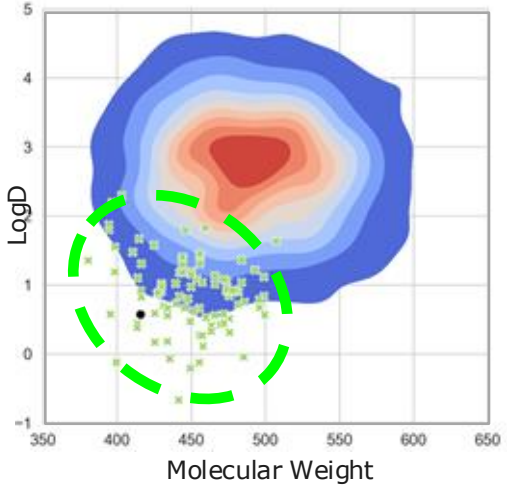
Proprietary structural insight → **AI-enabled design** → **Novel, tractable space**



- Pocket was **unknown**
- **Molecular dynamics simulations** to explore protein flexibility, **revealing a novel pocket**



- Generative 3D evolution targeting novel interactions and **synthetic feasibility**



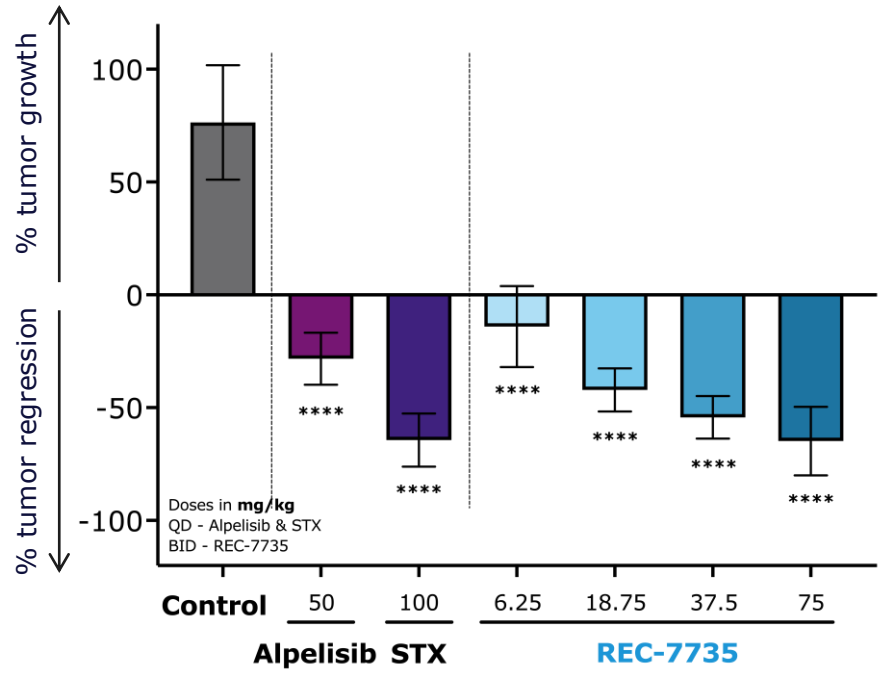
- Rapid design cycles exploring potency and ADMET space
- Highly novel, low MW & logD series with **good potency and exquisite selectivity**

From 1st novel hit to REC-7735:
242 compounds synthesized – 13 cycles – 10 months

Recursion

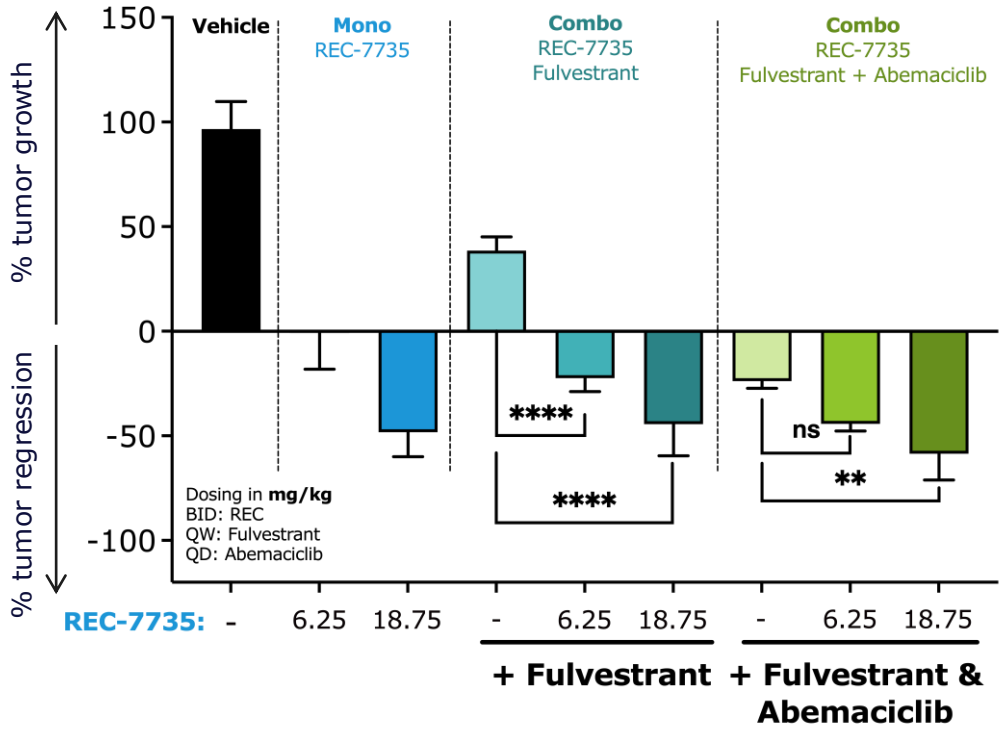
Demonstrates activity in preclinical model and potential combination approach with SoC[1]

Dose-dependent tumor regression[2]



- A separate preclinical study[3] also showed improved tumor regression with lower dose REC-7735 against high-dose capivasertib

Outperforms & synergizes SoC[1,4]
Fulvestrant (SERD) ± abemaciclib (CDK4/6i) combo

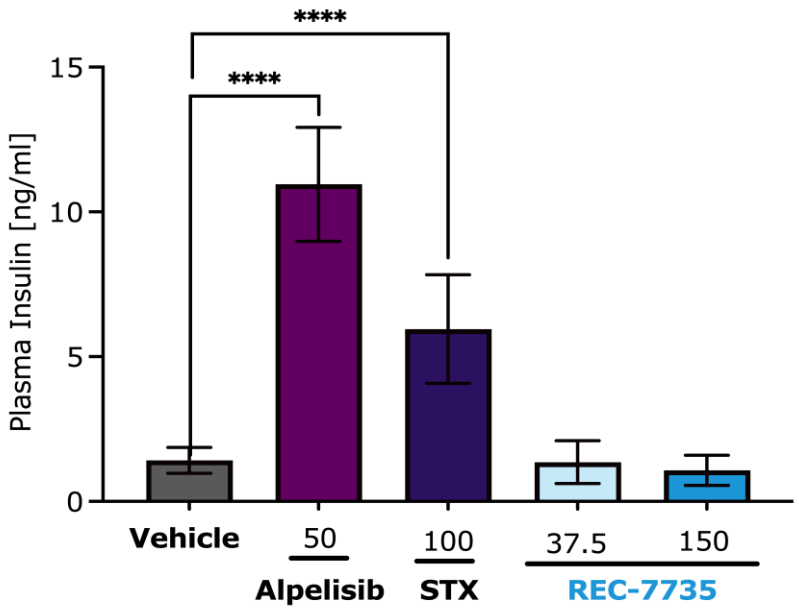


1. Fulvestrant (SERD) alone and or in combination with Abemaciclib (CDK4/6i) is used in HR+/HER2- advanced or metastatic breast cancer.
2. In vivo CDX Model using T47D (PI3Kα H1047R mutant) cell line. n=10 mice per group. Data represents tumor growth inhibition and regression after 14 days of dosing. Pharmacokinetic (plasma and tumor) and pharmacodynamic (tumor pAKT) data were consistent with the observed tumor growth inhibition and regression.
3. In vivo CDX Model using T47D (PI3Ka H1047R mutant) cell line. n=8 mice per group. REC-7735 (18.75mg/kg BID) achieved average tumor regression of -57%, Capivasertib (100mg/kg BID) achieved tumor regression of -11%.
4. In vivo CDX Model using T47D (PI3Kα H1047R mutant) cell line. n=8 mice per group. Data represents tumor growth inhibition and regression after 14 days of dosing.

Recursion

Limited/no impact on hyperglycemia markers in naïve or obese, diabetic animal models

No increase in hyperglycemia markers in naive WT mice[1]



Avoids hyperglycemia and metabolic liability at efficacious exposure in obese, diabetic rats[2]

	Vehicle	Alpelisib[3]		STX-478[3]		REC-7735[3]	
		8.25 mg/kg	25 mg/kg	33.3 mg/kg	100 mg/kg	100 mg/kg	300 mg/kg
Blood Glucose [mmol/L]	8.4	18.8	24.1	14.3	20.8	7.8	10.9
Plasma Insulin [ng/ml]	10.0	20.7	19.2	13.1	14.8	9.0	9.5
Serum C-Peptide [ng/ml]	16.2	25.2	21.6	19.5	19.8	15.2	16.1
L-Lactate [µmol/L]	5470	5041	3748	5223	4294	5418	4674
Ketone Bodies [mM]	0.1	0.1	2.3	0.1	0.8	0.2	0.1
Body Weight Change[4]	+3%	-3%	-13%	-3%	-21%	+3%	+1%

Compared to vehicle ns p<0.05 p<0.01

Note: Doses represented as mg/kg

1. In vivo naive wild-type, non-tumor bearing mice. n=6 mice per group. Data represents plasma insulin after 5 days of dosing. To note, plasma glucose and serum C-peptide, an inflammation marker, showed similar trends.
2. Heat map represents significant difference from vehicle based on average value of N=3 rats per treatment over 3 days of administration (green = ns, amber: p<0.05, red: p<0.01)
3. Alpelisib: 8.25mg/kg sub-efficacious dose, 25mg/kg approaching efficacious dose; STX-478: 33.3 mg/kg efficacious dose, 100mg/kg supra efficacious dose; REC-7735: 100mg/kg efficacious dose, 300mg/kg supra efficacious dose
4. Change in body weight between baseline and final measurement at day 5

Recursion

Potential to expand the treatable population through improved therapeutic index

Current PI3Kα inhibitors (SoC)

~11,000
of HR+, HER2- BC population

Tolerability-driven limitations:

65-85% Experienced hyperglycemia[1,2]

66-69% Dose interruption[1,2]

14-55% Dose reduction[1,2]

3-6 mos Real-world median time to discontinuation[3]

REC-7735 expansion opportunity through improved therapeutic index

>21,000
Across HER2+ BC, TNBC, colorectal, endometrial & uterine, and ovarian

If tolerability improves:

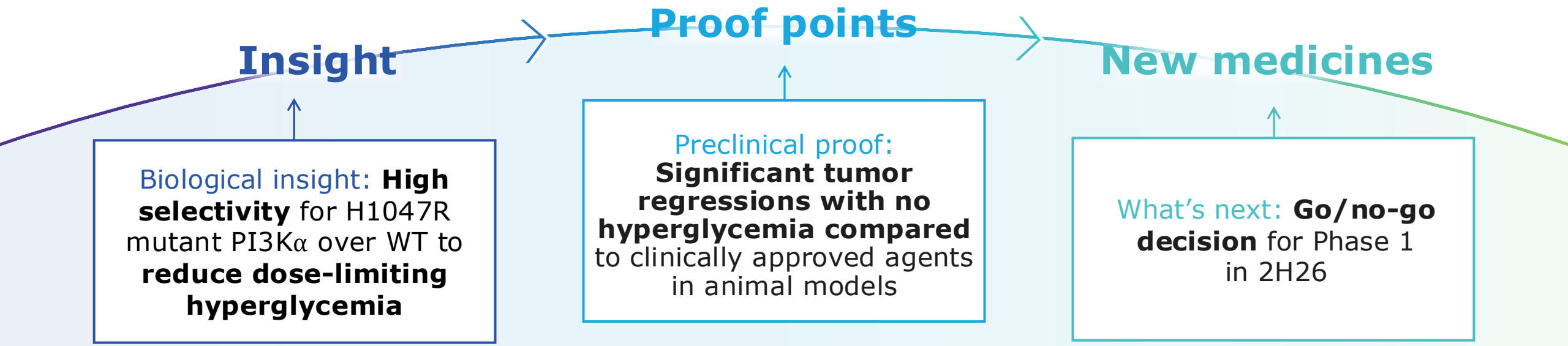
- Broader patient eligibility
- Longer treatment duration
- Expanded combination potential

Clinical validation of improved tolerability required to confirm expansion thesis

1. ITOVEBI FDA Label
2. PIQRAY FDA Label; Narayan P et al. *Clin Cancer Res* (2021) 27 (7): 1842–1849
3. Cross-sectional, Kaplan-Meier analysis of a large administrative health insurance database, calculating time from first exposure to discontinuation for currently approved PI3K inhibitors; median time to discontinuation suggests 50% continue with treatment in this timeframe

Recursion

REC-7735 (PI3Kα H1047Ri): Precision designed molecule aimed at achieving better outcomes



Recursion