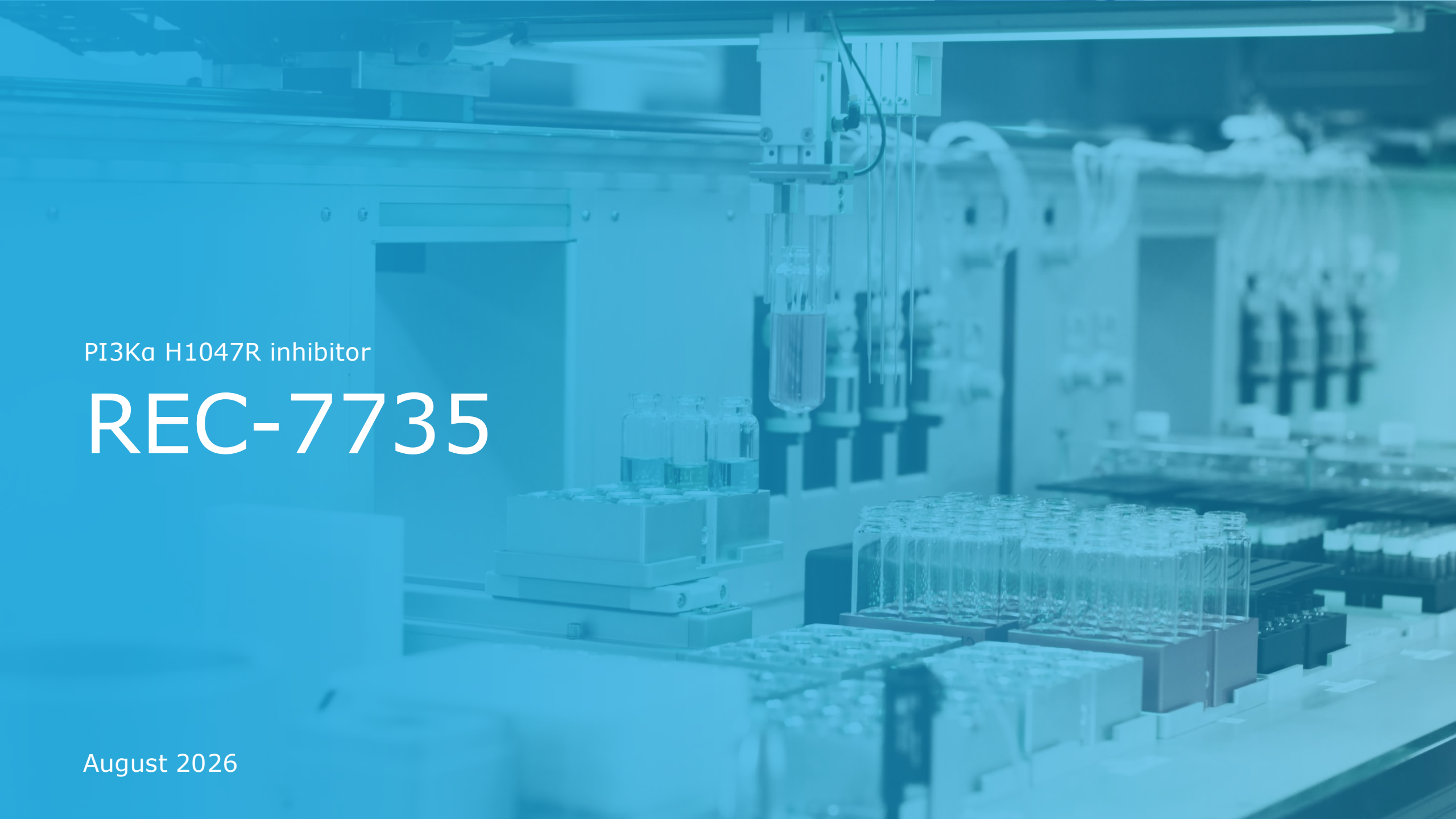


PI3Kα H1047R inhibitor

REC-7735

August 2026

Recent pan-mutant PI3Kα inhibitors still have suboptimal therapeutic index

PI3Kα is a validated target but wildtype inhibition drives hyperglycemia and tolerability issues that limit efficacy

A validated oncology target[1]

PI3Kα-H1047R mutation is a validated driver across multiple cancers; H1047R mutations make up the largest, distinct subtype among PIK3CA-driven cancers

Wildtype inhibition drives toxicity[2]

Next-gen Pan-mutant inhibitors also block wildtype PI3Kα, which can drive tolerability issues and hyperglycemia (grade 1/2 hyperglycemia)

Hyperinsulinemia can reactivate PI3K in the tumor[3]

WT-driven hyperglycemia triggers compensatory hyperinsulinemia — which can reactivate PI3K signaling within the tumor, undercutting efficacy independent of dose or tolerability

Toxicity forces dose compromises[2,4]

Toxicity-driven dose interruptions and discontinuations, which can prevent patients achieving optimal pathway inhibition

WHAT WE'RE HEARING FROM KOLS

> ***"We have to move away from the idea that Grade 1 hyperglycemia is 'fine.'*** *Even at low levels, the accompanying hyperinsulinemia can reactivate the PI3K pathway within the tumor" – KOL*

> ***"The biggest unmet need is the diabetic patient****. We are still excluding the 20% of the population that arguably needs these drugs most because we haven't uncoupled the tumor's PI3K from the liver's glucose control" – KOL*

1. Madsen et al. Oncogenic *PIK3CA* promotes cellular stemness in an allele dose-dependent manner, *Proc. Natl. Acad. Sci. U.S.A.* 116 (17) 8380-8389, https://doi.org/10.1073/pnas.1821093116 (2019) | Conditional activation of Pik3ca(H1047R) in a knock-in mouse model promotes mammary tumorigenesis and emergence of mutations. Oncogene. 2013 Jan 17;32(3):318-26. Epub 2012 Feb 27. https://doi.org/10.1038/onc.2012.53 | Distinction: L. Zhao & P.K. Vogt, Helical domain and kinase domain mutations in p110α of phosphatidylinositol 3-kinase induce gain of function by different mechanisms, *Proc. Natl. Acad. Sci. U.S.A.* 105 (7) 2652-2657, https://doi.org/10.1073/pnas.0712169105 (2008).
2. Hanker et al. *Cancer Discov* (2019) 9 (4): 482–491. https://doi.org/10.1158/2159-8290.CD-18-1175
3. Hopkins, B.D., Pauli, C., Du, X. *et al.* Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. *Nature* **560**, 499–503 (2018). https://doi.org/10.1038/s41586-018-0343-4
4. Shen S, Chen Y, Carpio A, Chang C, Iyengar NM. Incidence, risk factors, and management of alpelisib-associated hyperglycemia in metastatic breast cancer. *Cancer.* 2023; 129(24): 3854-3861. doi:10.1002/cncr.34928

Recursion

Our platform designed a mutant-selective PI3Kα H1047R inhibitor built to improve therapeutic index

REC-7735

>100x

selectivity for H1047R over wildtype

Precision for the mutation that matters most: H1047R is PI3Kα's single most frequent activating mutation

Platform identified a previously unpublished binding site and delivered a development candidate in only 10 months[1] with no identified off-target liabilities

Precision for H1047R turns >100x selectivity into a wider therapeutic index

A wider therapeutic index drives multiple benefits:

Deep target suppression

>100x selectivity drives full inhibition of H1047R at effective doses, potentially avoiding the toxicity ceiling that may require dose adjustments in pan-mutant inhibitors

Higher dose intensity & duration

Avoiding WT-driven toxicity lets patients stay on therapeutic doses longer, translating selectivity into deeper, more durable efficacy

Avoids hyperinsulinemia-driven reactivation

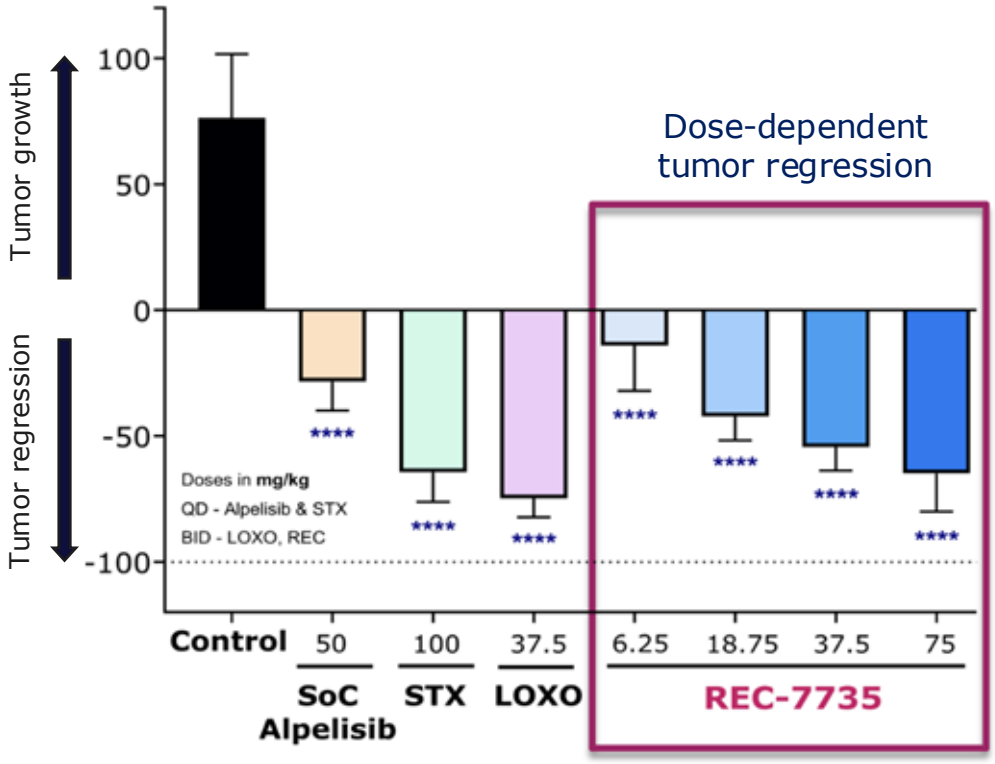
Limits the hyperinsulinemia that can reactivate PI3K signaling in the tumor and compromise efficacy, while easing treatment of prediabetic / diabetic patients

Preclinical proof: *dose-dependent tumor regression superior or comparable to other PI3Kα inhibitors with no hyperglycemia signal observed[2]*

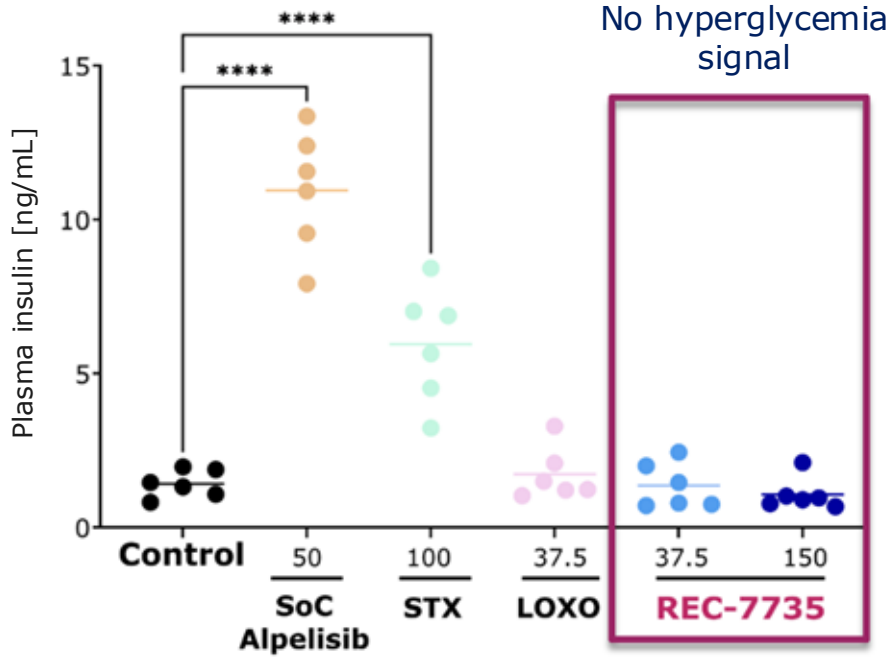
1. ~10 months from first hit to development candidate, across only 242 compounds
2. Results generated in a breast cancer CDX model with an H1047A mutant PI3Kα and in naïve wildtype mice

REC-7735: Potent tumor regression without hyperglycemia in preclinical models

1 ***Efficacy superior or comparable*** *to Alpelisib & STX-478*[1]



2 ***Lowest increase in hyperglycemia markers*** *among comparators*[2]



1. Results generated in a breast cancer CDX model with a H1047A mutant PI3Kα 2. Results generated in naïve wildtype mice

Recursion

Highly mutant-selective PI3K inhibitors with an improved TI have potential to benefit a greatly expanded patient population

Improved outcomes for indications with PI3Kα inhibitors

Ability to **treat additional indications** not reached by current therapies due to insufficient depth of inhibition, hyperglycemia, and tolerability

H1047R HR+ / HER2- breast cancer, across stages

- Pan-mutant PI3Kα inhibitors
- Tolerability concerns limit treatment duration, potentially reducing efficacy
- Historically, treatment has been mostly limited to non-diabetic and carefully selected, well-controlled diabetic patients due to hyperglycemia

~47,000 Patients[1] | **~16-21%** Diabetic[1]

H1047R metastatic solid tumors

- Including HER2+ BC, TNBC, colorectal, endometrial, ovarian, and head & neck cancers
- Hyperglycemia and tolerability concerns limit may limit treatment duration

~12,000 Patients | **~16-30%** Diabetic[2]

H1047R non-metastatic solid tumors

- Including HER2+ BC, TNBC, colorectal, endometrial, ovarian, and head & neck cancers
- Longer treatment duration in lower disease-burden patients raises tolerability requirements

~21,000 Patients | **~9-20%** Diabetic[2]

H1047R-driven non-onc. conditions

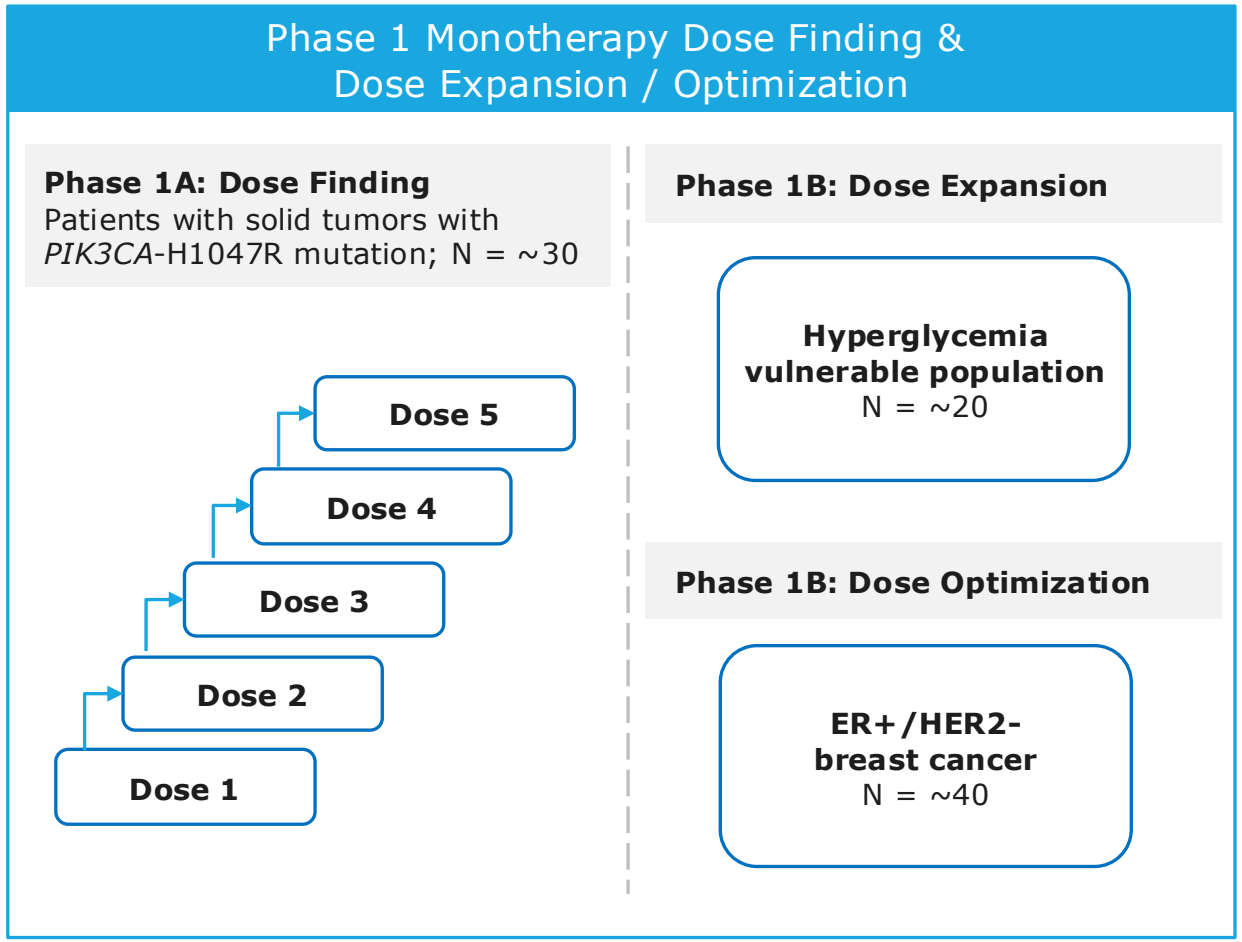
- Including PROS and PIK3CA-related vascular anomalies
- Current approved treatment can cause hyperglycemia, potentially limiting efficacy

~25,000 Patients

Note: TAM in US + EU5 for indications with H1047R mutations

1. Inclusive of early stage & metastatic cancer patients
2. % varies dependent on solid tumor indication

Phase 1 Dose Finding Clinical Trial: ZINNIA Phase 1/2 trial in patients with *PIK3CA* H1047R-mutant select solid tumors



- **Combination expansion** will be based on clinical safety profile and target engagement
- **Leveraging RWD** to optimize protocol and expand eligible patient population

Next steps:

- Initiate ZINNIA trial in 2H26
- Early safety and PK from monotherapy trial in 1H28

Recursion