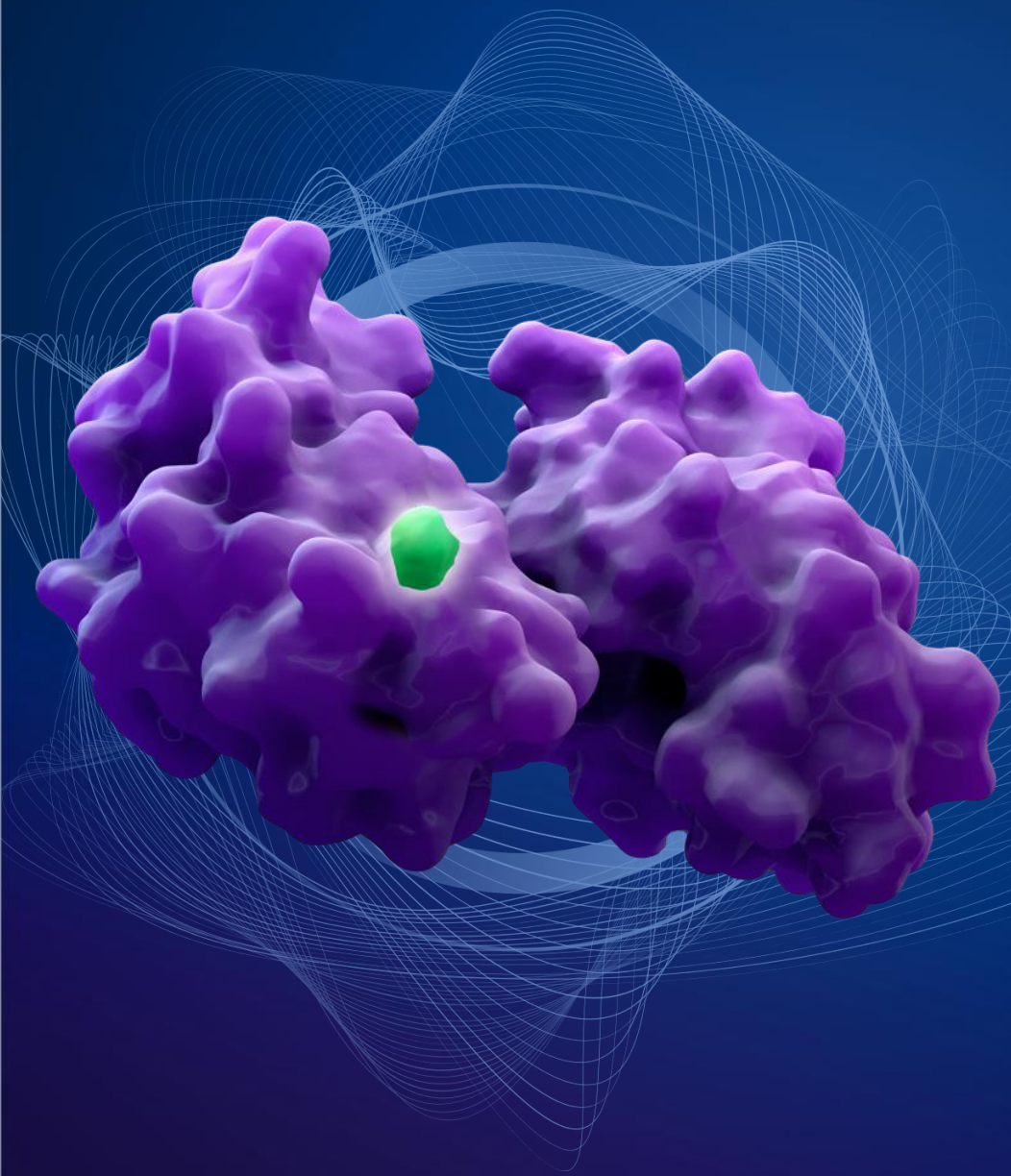


ENSEM THERAPEUTICS

Accelerating Small Molecule Drug Discovery via AI-Powered Kinetic Ensemble® Platform

Shengfang Jin, PhD

CEO and Co-Founder

ENSEM is Expanding the Universe of Druggable Targets to Bring Transformative Therapies to Patients

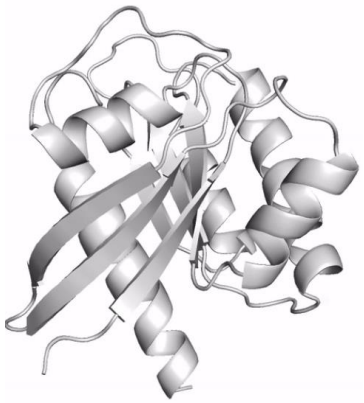
- Substantial **challenges** exist in small molecule drug discovery in high-value but difficult-to-drug targets
- **Kinetic Ensemble®,** ENSEM's deep learning AI platform, addresses these challenges and has enabled a clinical-stage **proprietary precision medicine** pipeline in three years
  - CDK2 inhibitor in Phase 1 (partnered with BeiGene, with a total deal value ~$1.33B + royalty)
  - Pan-mutant PI3Ka **dual** inhibitor/degrader to file IND and initiate Phase 1 in 1H 2025
- Seasoned industry leaders and "drug hunters"
- Strong financial backing: $120M* raised since inception in 2021
- **Multiple value inflection points** in the next 24 months

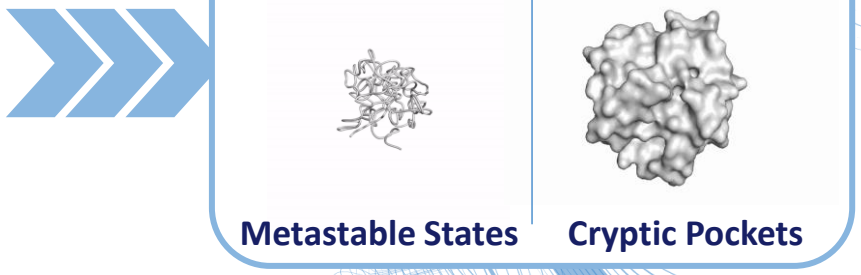
*include equity + nondilutive funding

ENSEM THERAPEUTICS

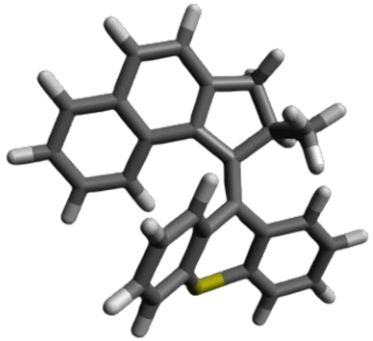
Kinetic Ensemble® Delivers Solutions for Difficult-to-Drug Targets

Difficult-to-Drug Target





Transformative Medicine



ENSEM THERAPEUTICS

Rapid Development of Precision Medicine Pipeline in 3 Years

Derisked with Biologically Validated and Clinically Translatable Programs

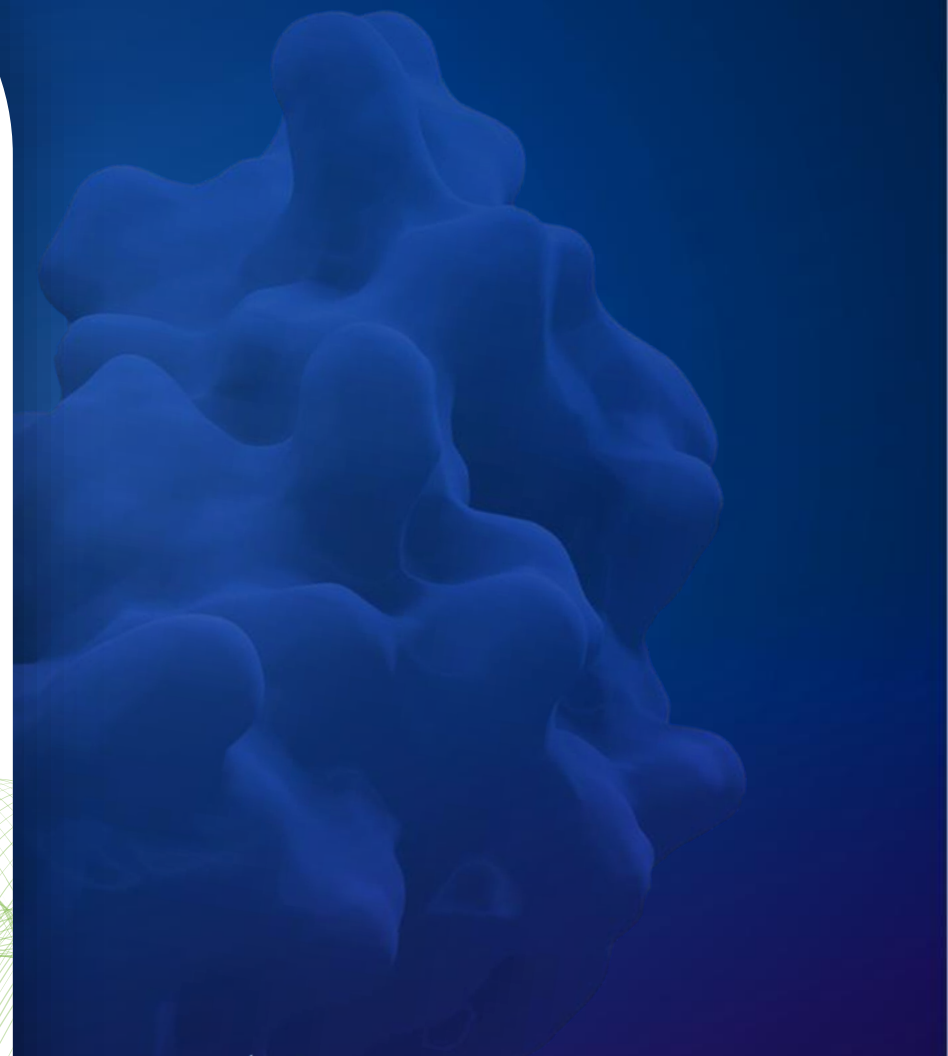
TARGET	PROGRAM	INDICATION	PRECLINICAL	IND	PHASE I	GLOBAL RIGHTS
CDK2	ETX-197/ BG-68501	Oncology				BeiGene, ENSEM THERAPEUTICS
Pan Mutant PI3Kα	ETX-636	Oncology & Rare Disease				ENSEM THERAPEUTICS
Synthetic Lethal Target	undisclosed	Oncology				ENSEM THERAPEUTICS
Oncogenic Driver	undisclosed	Oncology				ENSEM THERAPEUTICS

ENSEM THERAPEUTICS

ETX-197:
Best-in-Class CDK2 Inhibitor

Concept to IND in 2 Years

- ***1st Program discovered using Kinetic Ensemble®***
- ***Overcomes suboptimal potency, selectivity, and/or drug-like properties of current and emerging CDK2 therapies***
- ***Partnered with BeiGene***



ENSEM THERAPEUTICS

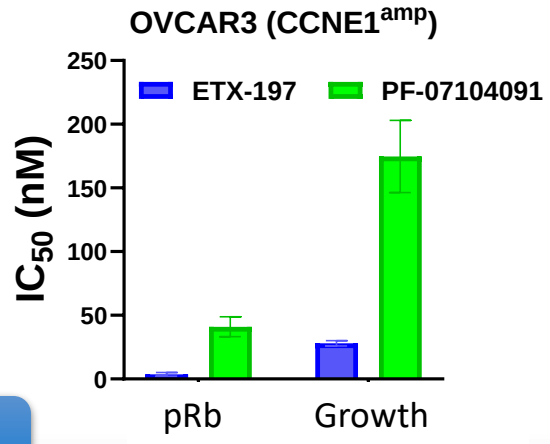
ETX-197: Potentially Best-in-Class CDK2 Inhibitor in the Clinic

Best-in-Class Biochemical Potency and Selectivity

Biochemical Potency CDK2:CycE1	ETX-197	PF-07104091
IC_{50} (nM)	0.93	3.8

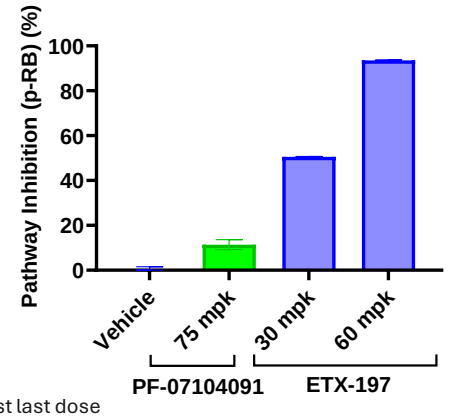
ETX-197 has 100-600 fold selectivity over other CDK family members

Superior Cellular Potency



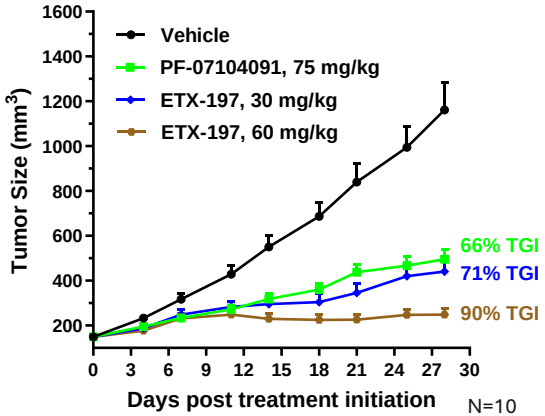
ETX-197

Potent Pathway Inhibition



*12h post last dose
Day 4 of oral dosing

Robust *In Vivo* Activity



OVCAR3 Ovarian Xenografts

N=10
BID dosing, P.O.

Partnered with BeiGene

ETX-197/BG-68501 currently in FIH studies

- Monotherapy in advanced solid tumors
- Combination with fulvestrant ± BGB-43395 (CDK4i) in HR+/HER2- breast cancer

www.clinicalTrials.gov (NCT06257264)

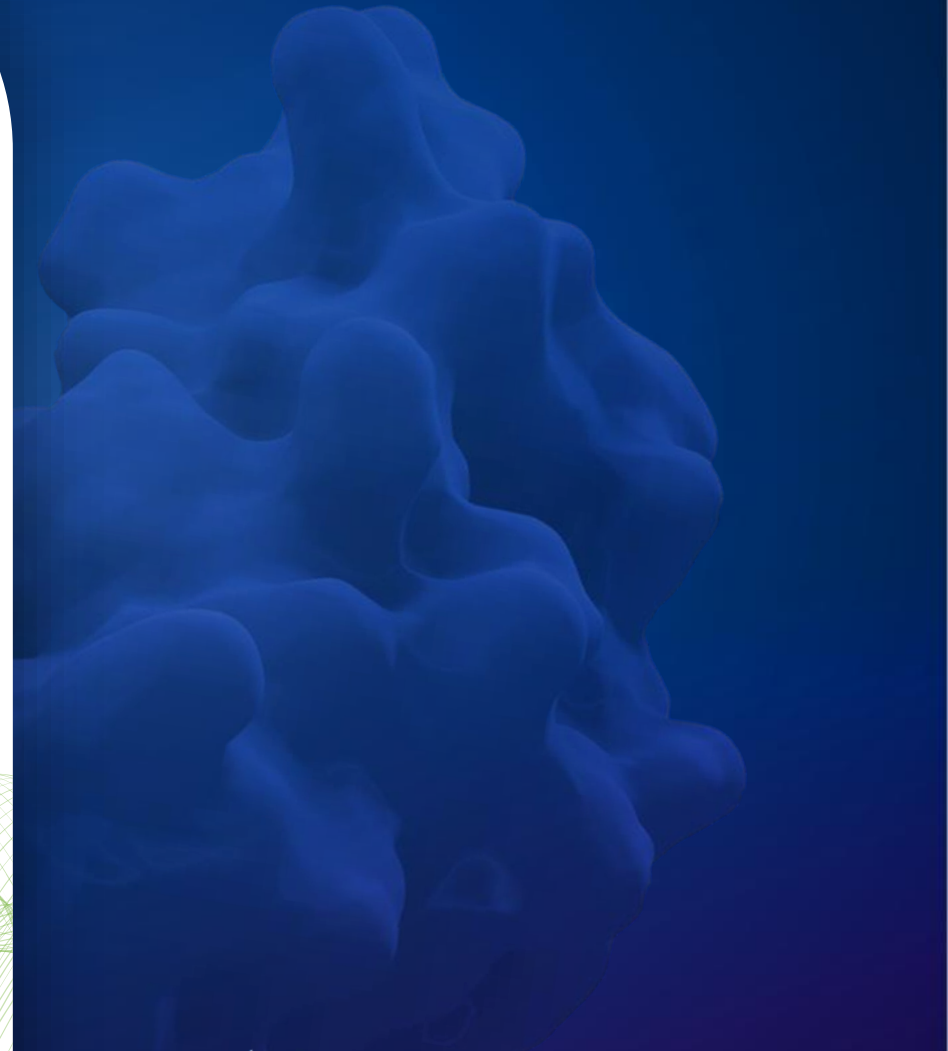
Banerjee et al SABCS Annual meeting 2024; Barve et al SABCS Annual meeting 2024

ENSEM THERAPEUTICS

ETX-636:
Next Generation Pan-Mutant Selective Allosteric Inhibitor and Degrader of PI3Kα

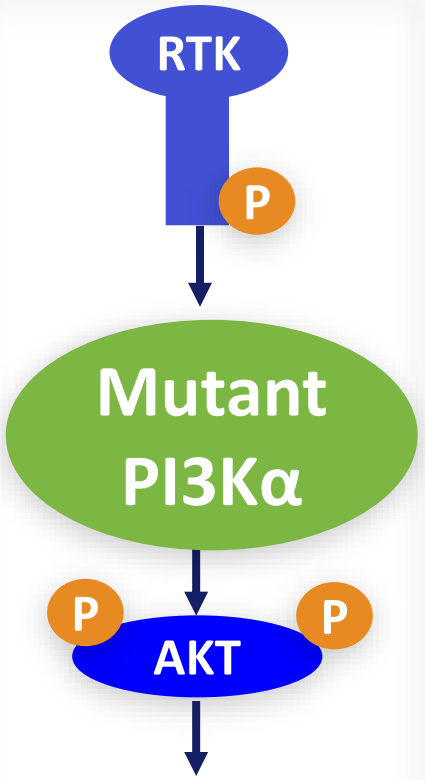
Concept to IND submission in 3 years

Allosteric Inhibition + Protein Degradation = Best-in-Class



ENSEM THERAPEUTICS

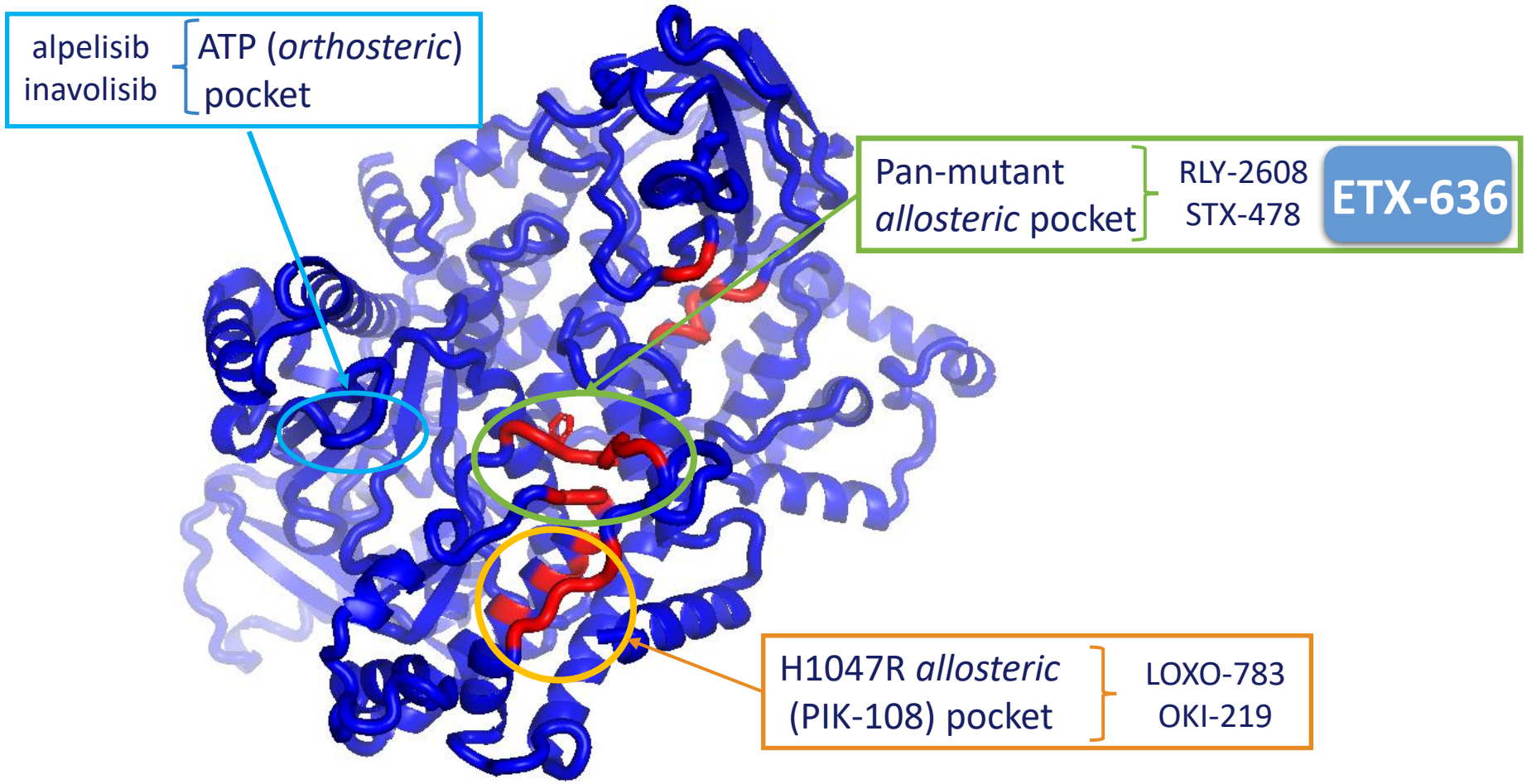
Kinetic Ensemble® Prioritizes a Specific PI3Kα Allosteric Pocket



Tumorigenesis

Large Validated Market
Significant Unmet Need

Catalytic Subunit of PI3Kα, p110α, and its three pockets for drug design



ETX-636 Delivers Solutions to Deficiencies of PI3Kα Clinical Agents

Issues with currently approved & emerging PI3Kα inhibitors	Desired Target Drug Profile

• **Orthosteric** ATP-pocket inhibitors (e.g., alpelisib, inavolisib)
  ○ Lack mutant/wildtype selectivity which undercuts efficacy
  ○ Low tolerability (e.g., hyperglycemia), limited clinical utility
	• >10x selectivity for mutant vs wild type PI3Kα to improve tolerability, efficacy and broaden patient population

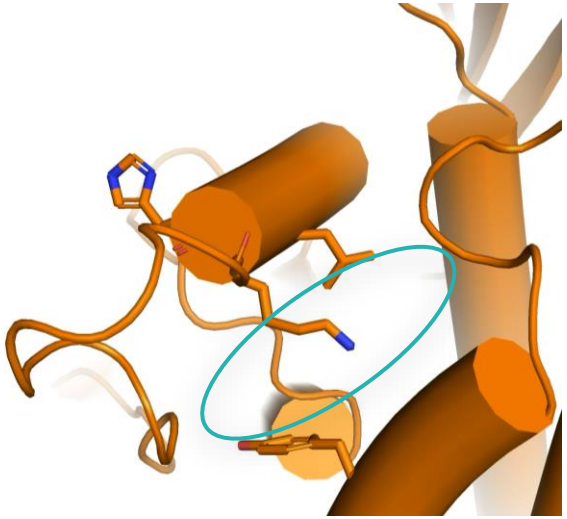
• **Allosteric** inhibitors (e.g., RLY-2608, STX-478, OKI-219) ○ Suboptimal *in vitro*, *in vivo* potency and/or drug properties	• Improved efficacy resulting from superior potency and better drug properties
• PI3Kα inhibition triggers **compensatory** feedback loop • ATP pocket mutations create **resistance** to orthosteric inhibitors	• **DUAL** allosteric inhibition and degradation of mPI3Kα to abrogate compensatory feedback and overcome drug resistance

ETX-636 Is a Differentiated Next Generation Dual PI3Kα Inhibitor & Degrader
- Allosteric & Pan-Mutant Selective

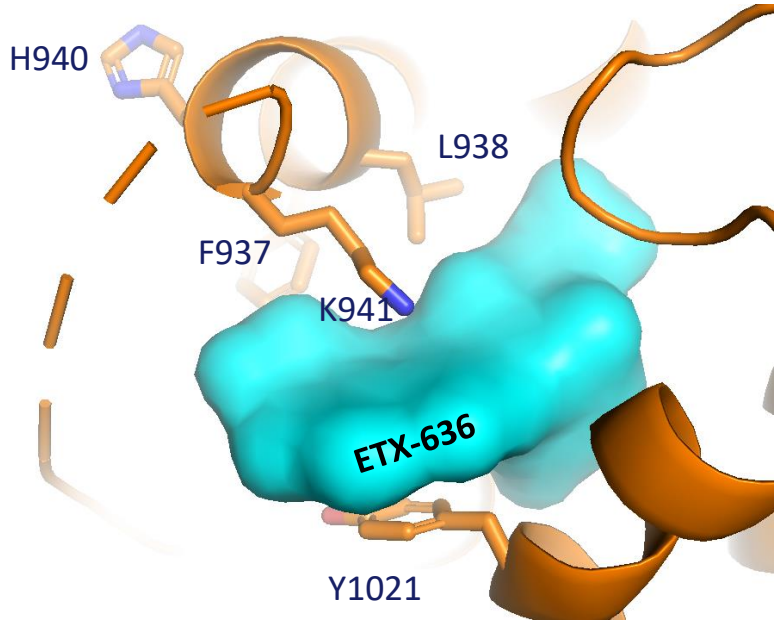
ENSEM THERAPEUTICS

EnsemGen® Elucidated a Unique PI3Kα Conformation Enabling ETX-636 Design

EnsemGen® Simulation



Chemical Design Targets This Metastable State



Mutant PI3Kα activation loop dynamics & most stable inhibitory conformation

ETX-636 differentiated binding pose in allosteric pocket

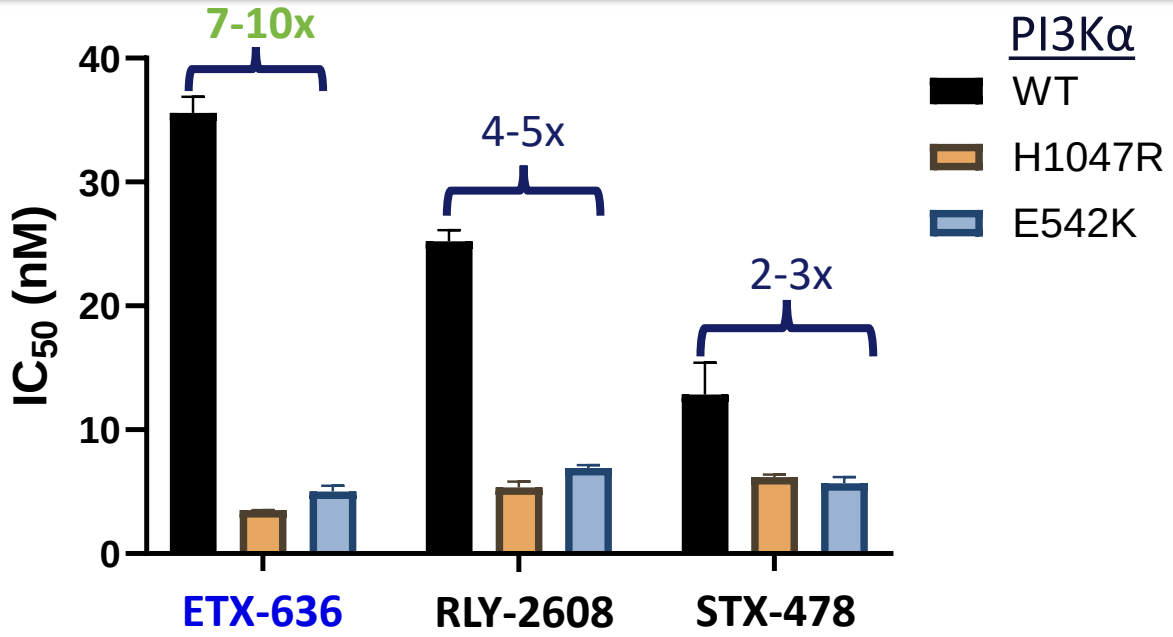
1. Delivers **tight binding to a unique metastable state** -> slowest off-rate and longest residence time

2. Selectively captures mutant PI3Kα in the **metastable** state -> **degradation** of mutant PI3Kα in cells

ENSEM THERAPEUTICS

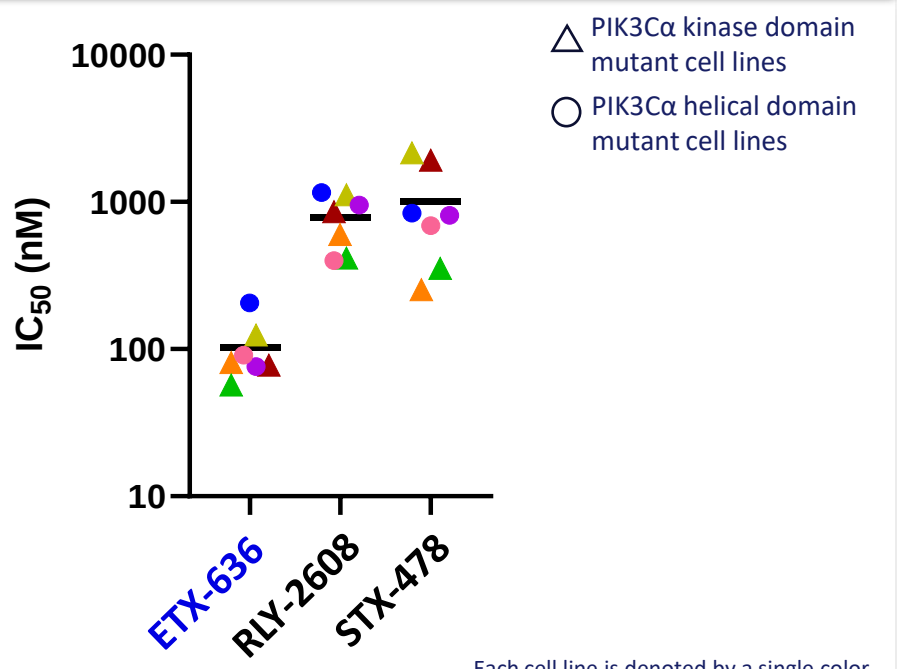
ETX-636 Demonstrates Superior Potency and Selectivity for Mutant PI3Kα

Biochemical Activity



ETX-636 IC_{50}s for PI3Kβ/γ/δ are ≥ 10μM.

Cancer Cell Viability



Each cell line is denoted by a single color

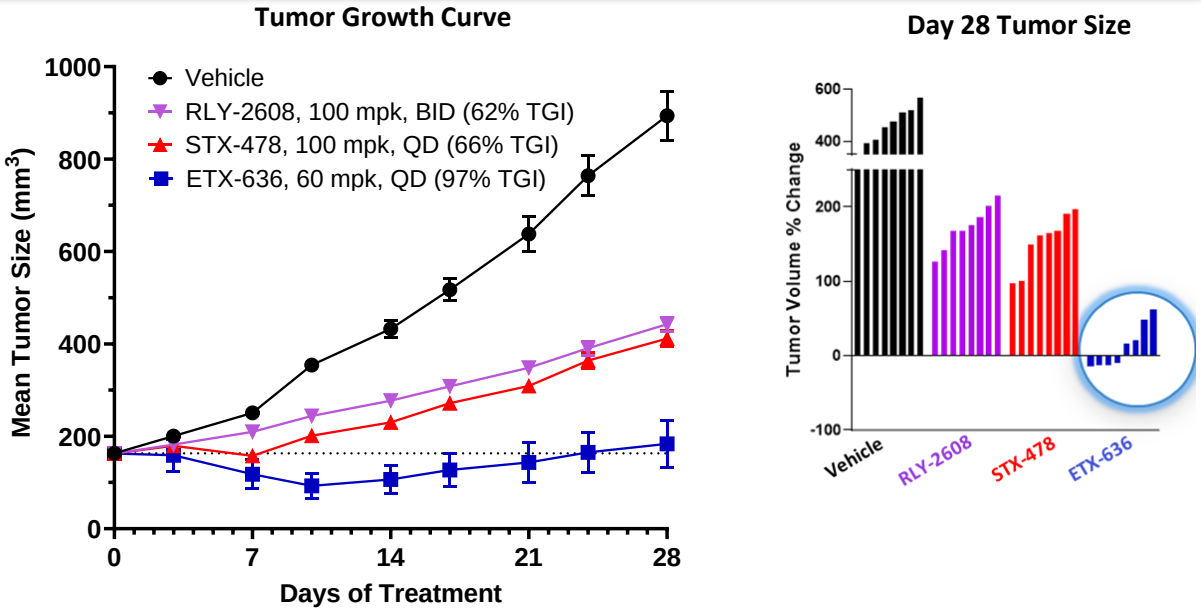
- ETX-636 potently inhibits both kinase and helical domain hotspot mutations and other PI3Kα activating mutations
- ETX-636 demonstrates good concordance with its biomarker (pAKT) and cell growth (CTG) potencies

ENSEM THERAPEUTICS

ETX-636 Shows Superior In Vivo Efficacy and PI3Kα Pathway Inhibition

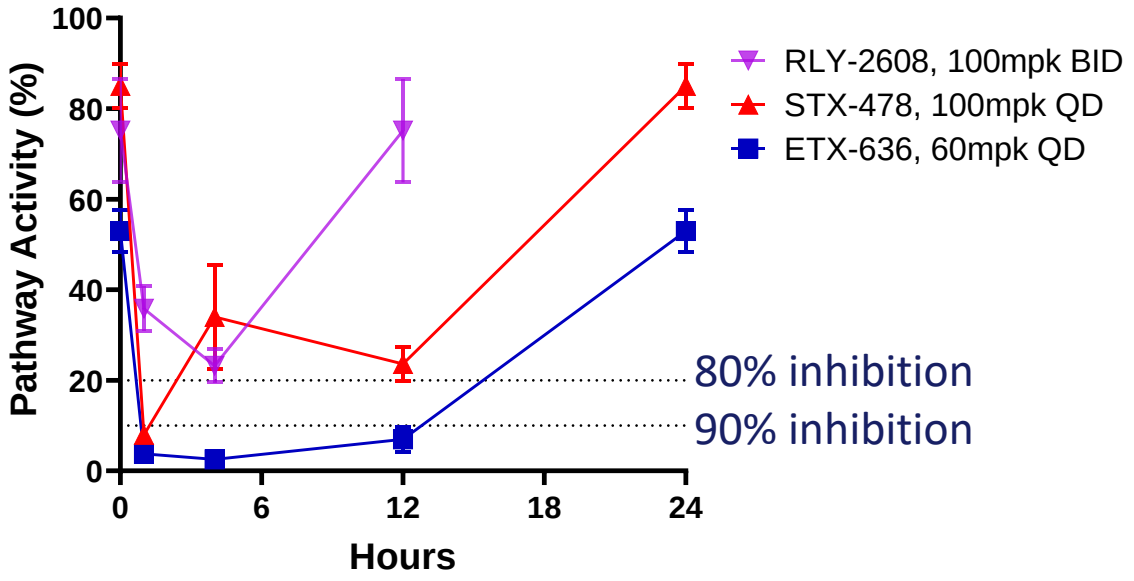
Greater Preclinical Anti-tumor Growth Inhibition

HR-/HER2+ CDX Breast Cancer with PI3Kα Mutation



Deeper and More Durable Pathway Inhibition

pAKT in CDX Tumors



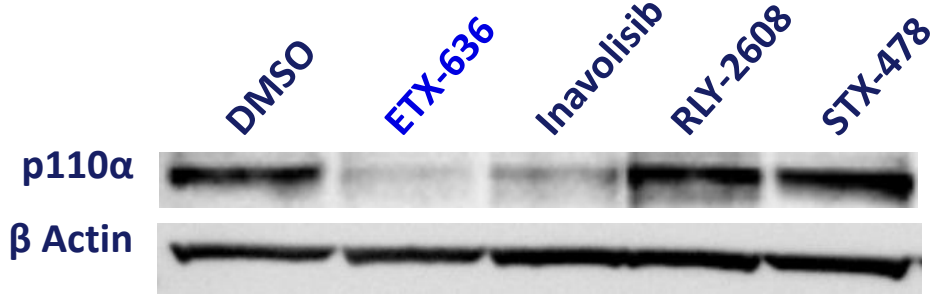
- ETX-636 does not impact glucose homeostasis at efficacious doses in experimental animals
- ETX-636 demonstrates good concordance of drug exposure, biomarker (pAKT) and tumor growth inhibition (TGI)

Studies conducted using HCC1954 , an HR-/HER2+ Breast Cancer cell line harboring PIK3CA kinase domain (H1047R) mutation, similar observation in helical domain mutants.
CDX = cell line-derived tumor xenograft. mpk=milligram per kilogram; QD = daily dosing; BID=twice a day dosing

ENSEM THERAPEUTICS

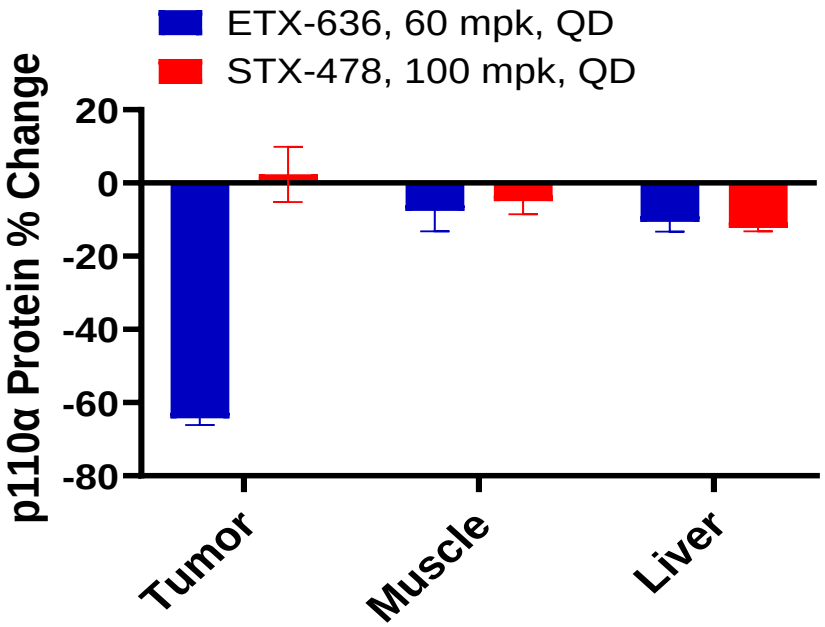
ETX-636 Selectively Degrades Mutant PI3Kα, Sparing Wildtype

ETX-636 Degrades Mutant PI3Kα Protein in Cancer Cell Lines *in vitro*



Assessment of protein levels post compound treatment

ETX-636 Degrades Mutant PI3Kα in CDX Tumors but not Wildtype PI3Kα in Healthy Tissues *in vivo*



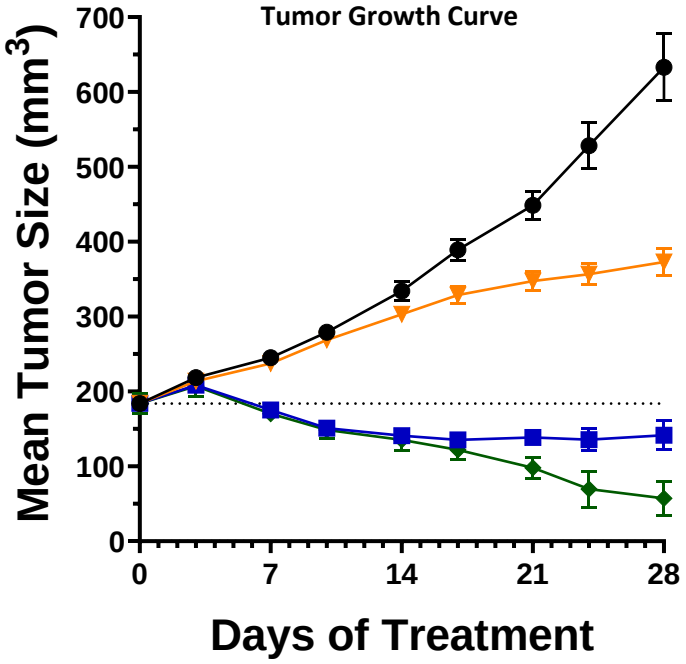
Loss of Mutant PI3Kα contributes to superior depth and durability of pathway abrogation (pAKT) and concordant tumor growth inhibition

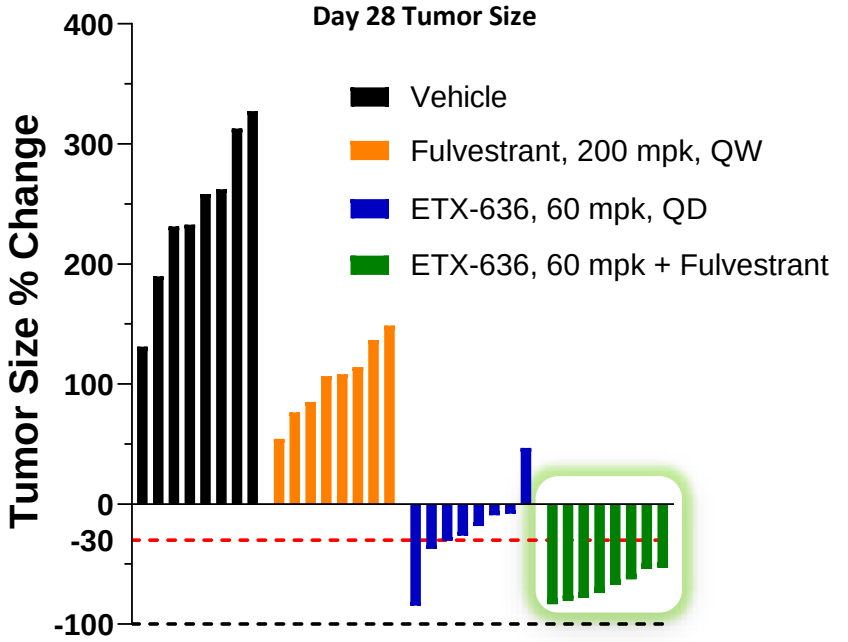
HCC1954, HR-/HER2+ PIK3CA H1047R breast cancer cell line, with a mutant variant allele frequency of 0.79
Similar observations are seen in PIK3CA helical domain mutant cancer cells. mpk=milligram per kilogram; QD = daily dosing

ENSEM THERAPEUTICS

ETX-636 Combination with Fulvestrant Demonstrates Synergy and Supports Targeting 2nd Line Advanced Breast Cancer

HR+ Her2- Breast Cancer Model Harboring PI3Kα Mutation





Study conducted with MCF7, an HR+/HER2- breast cancer cell line harboring PIK3CA helical domain (E545K) mutation
mpk=milligram per kilogram; QD = daily dosing; QW = once a week dosing

ENSEM THERAPEUTICS

ETX-636 Is a Differentiated Next Generation Dual PI3Kα Inhibitor & Degrader

Allosteric & Pan-Mutant Selective

Issues with currently approved & emerging PI3Kα inhibitors	ETX-636 Drug Profile	

• **Orthosteric** ATP-pocket inhibitors (e.g., alpelisib, inavolisib)
  ○ Lack mutant/wildtype selectivity which undercuts efficacy
  ○ Low tolerability (e.g., hyperglycemia), limited clinical utility
	• >10x selectivity for mutant vs wild type PI3Kα to improve tolerability, efficacy and broaden patient population	✔

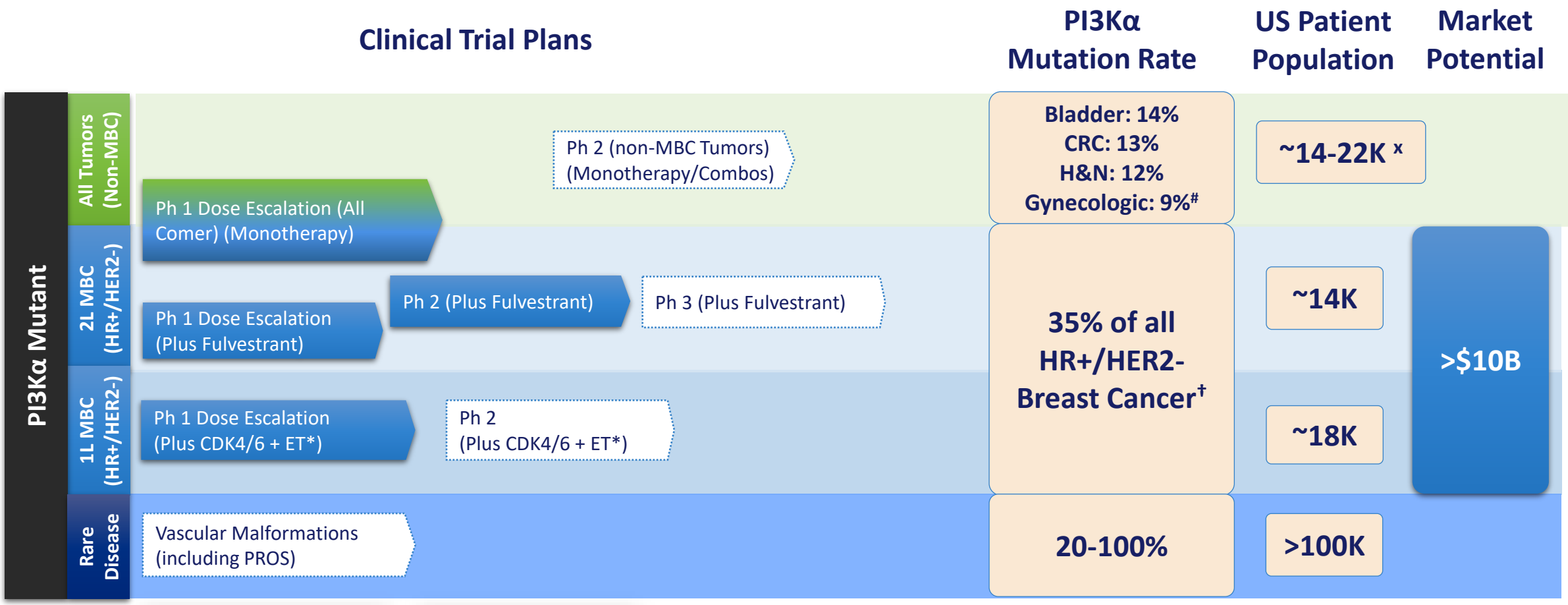
• **Allosteric** inhibitors (eg, RLY-2608, STX-478, OKI-219) ○ Suboptimal *in vitro*, *in vivo* potency and/or drug properties	• Improved efficacy resulting from superior potency and better drug properties	✔
• PI3Kα inhibition triggers **compensatory** feedback loop • ATP pocket mutations create **resistance** to orthosteric inhibitors	• **DUAL** allosteric inhibition and degradation of mPI3Kα to abrogate compensatory feedback and overcome drug resistance	✔

Projected to achieve PI3Kα target/pathway coverage above IC_{90} for up to 24hrs *without* impacting glucose homeostasis in the clinic

ETX-636: Potential to Achieve Superior Clinical Activity Over All Competitors PI3Kαi

ENSEM THERAPEUTICS

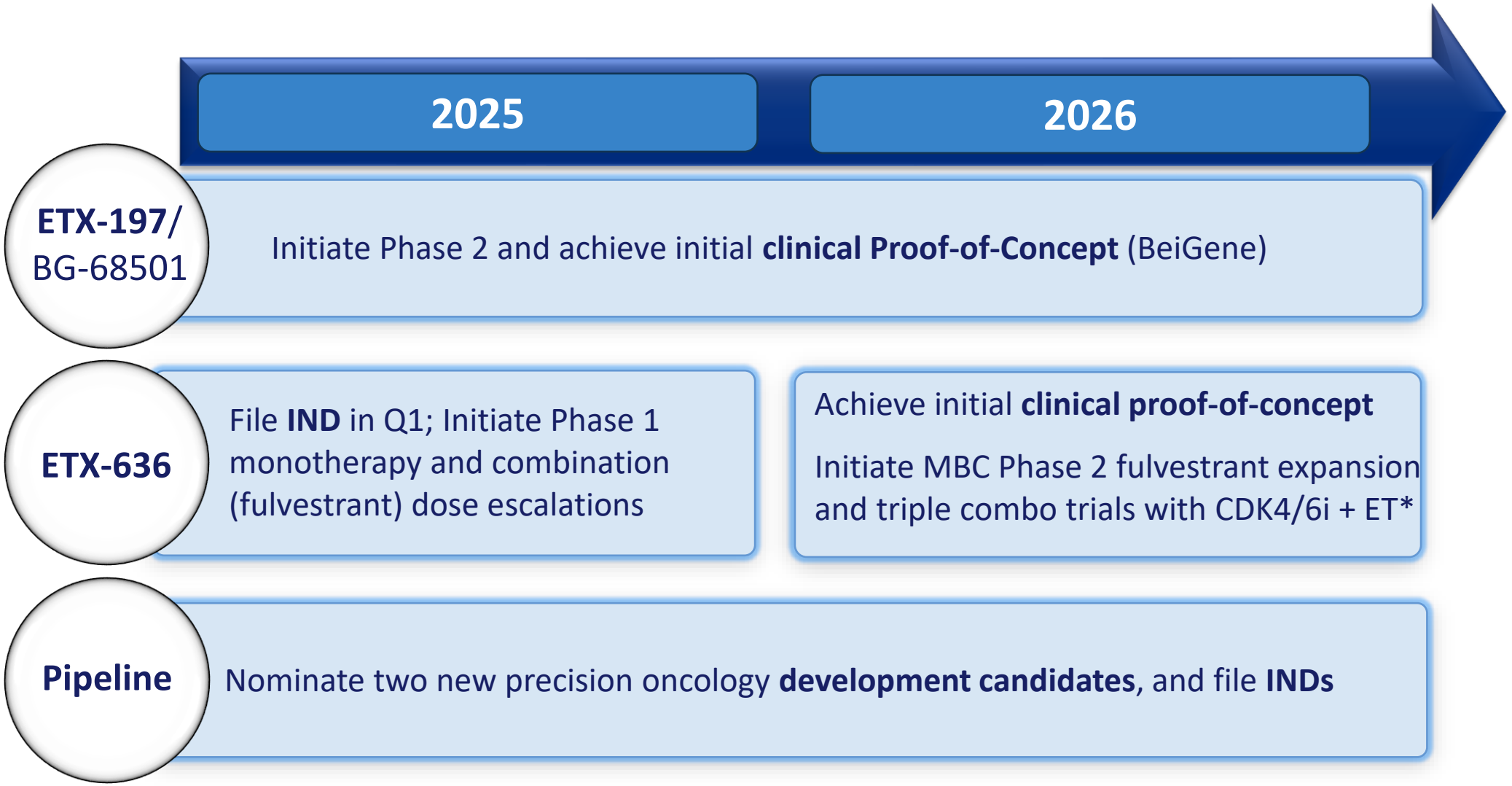
ETX-636: Excellent Potential for Diseases Driven by PI3Kα Mutations



*ET: Endocrine therapy which could include SERDS/PROTACs and aromatase inhibitors
†Ensem's internal assessment using breast cancer incidence data from SEER
PI3Kα mutation rate estimation based on hotspot PI3Kα mutations with wild-type AKT and PTEN
x patient population for non-breast cancers is estimated based on TCGA advanced-stage cancer, annual cancer incidence and death from American Cancer Society 2021 report and only includes the four non-Breast cancers listed here.

ENSEM THERAPEUTICS

Multiple Value Inflection Points in 2025 and Beyond



ENSEM THERAPEUTICS

ENSEM is Expanding the Universe of Druggable Targets to Bring Transformative Therapies to Patients

- Substantial **challenges** exist in small molecule drug discovery in high-value but difficult-to-drug targets
- **Kinetic Ensemble®,** ENSEM's deep learning AI platform, addresses these challenges and has enabled a clinical-stage **proprietary precision medicine** pipeline in three years
  - CDK2 inhibitor in Phase 1 (partnered with BeiGene, with a total deal value ~$1.33B + royalty)
  - Pan-mutant PI3Ka **dual** inhibitor/degrader to file IND and initiate Phase 1 in 1H 2025
- Strong financial backing: $120M* raised since inception in 2021
- Seasoned industry leaders and "drug hunters"
- **Multiple value inflection point**s in the next 24 months

*include equity + nondilutive funding

ENSEM THERAPEUTICS

Dedicated to Making an Impact on Patient's Lives via Transformative Medicines

ENSEM THERAPEUTICS

Thank You

info@ensemtx.com

880 Winter Street, Suite 1003

Waltham, MA02451

USA

www.ensemtx.com

ENSEM THERAPEUTICS