OnKure® THERAPEUTICS

Selectivity Matters and Pan-Mutant Allosteric Inhibition Delivers

July 15, 2026

Legends

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding, OnKure's product candidates and programs, including OKI-355 and OKI-345; OnKure's ability to advance additional programs; expected milestones and the timing of such milestones, the submission of IND applications for OKI-355 and OKI-345; and statements regarding OKI-345 and OKI-355 as best-in-class. In some cases, you can identify forward-looking statements by terminology such as "expect," "estimate," "intend," "may," "plan," "potentially," "will" or the negative of these terms or other similar expressions.

These forward-looking statements are based largely on OnKure's current expectations and projections about future events and trends that OnKure believes may affect its financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: OnKure's limited operating history; the significant net losses incurred since inception; the ability to raise additional capital to finance operations; the risk that actual uses of cash and cash equivalents differ from the assumptions underlying OnKure's expected cash runway; the ability to advance product candidates through preclinical and clinical development; the ability to obtain regulatory approval for, and ultimately commercialize, OnKure's product candidates; the outcome of preclinical testing and early clinical trials for OnKure's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements and the potential that the outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials; OnKure's limited resources; the risk of adverse events, toxicities or other undesirable side effects; potential delays or difficulties in the enrollment or maintenance of patients in clinical trials; the decision to develop or seek strategic collaborations to develop OnKure's current or future product candidates in combination with other therapies and the cost of combination therapies; OnKure's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition OnKure faces in discovering, developing, or commercializing products; OnKure's ability to protect its intellectual property and proprietary technologies; developments relating to OnKure's competitors and its industry, including competing product candidates and therapies; reliance on third parties, contract manufacturers, and contract research organizations; legislative, regulatory, political and economic developments and general market conditions; and those risks described in the section entitled "Risk Factors" in documents that OnKure files from time to time with the SEC. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for OnKure's management to predict all risk factors, nor can OnKure assess the impact of all factors on OnKure's business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although OnKure believes that the expectations reflected in the forward-looking statements are reasonable, OnKure cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, OnKure undertakes no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

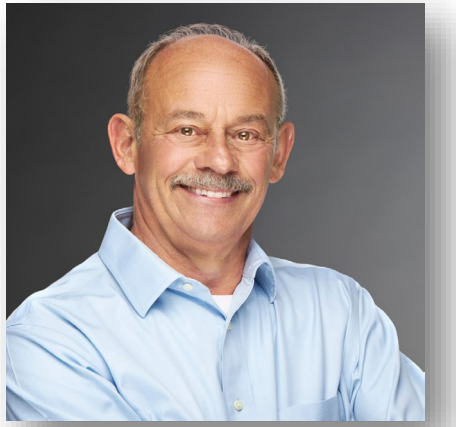
Agenda

Topic	Presenter
Welcome & Introduction	**Nicholas Saccomano, Ph.D.** *President & Chief Executive Officer of OnKure*
OnKure: A Differentiated Portfolio	
Targeting Cryptic Allosteric Pockets	**Benjamin Cravatt, Ph.D.** *Prof. of Chemistry and Norton B. Gilula Chair of Chemical Biology, Scripps Research*
The Pursuit of PI3Kα Therapeutic Selectivity	**Robert Abraham, Ph.D.** *Chief Scientific Officer at Engine Biosciences*
OnKure's Pipeline Strategy & Portfolio Overview	**Nicholas Saccomano, Ph.D.** *President & Chief Executive Officer of OnKure*
Q&A	

Today’s Guest KOLs

Benjamin F. Cravatt, Ph.D.

Professor of Chemistry and the Norton B. Gilula Chair of Chemical Biology at Scripps Research. A pioneer in chemical biology and proteomics, he has developed transformative technologies for protein and drug discovery and co-founded several biotechnology companies, including Vividion Therapeutics. He is a member of the National Academy of Sciences, and the recipient of the 2022 Wolf Prize in Chemistry.



Robert T. Abraham, Ph.D.

Chief Scientific Officer of Engine Biosciences and former head of Oncology R&D at Pfizer, where his teams advanced multiple clinical candidates and contributed to 11 FDA-approved oncology drugs. A pioneer in PI3K/mTOR biology, he has authored more than 230 scientific publications and serves as an advisor to leading biotechnology companies and Google Ventures.

OnKure is Developing a Differentiated Portfolio

OnKure Therapeutics

- **Developing PI3Kα PAN-mutant Inhibitors** with the highest known selectivity across helical and kinase mutations
- Two distinct candidates designed for **Vascular Anomalies & Cancer**
- Experienced R&D team to support portfolio expansion and application to vascular anomalies beyond PI3Kα inhibition

Portfolio

Two Lead PI3Kα^{PAN} Programs

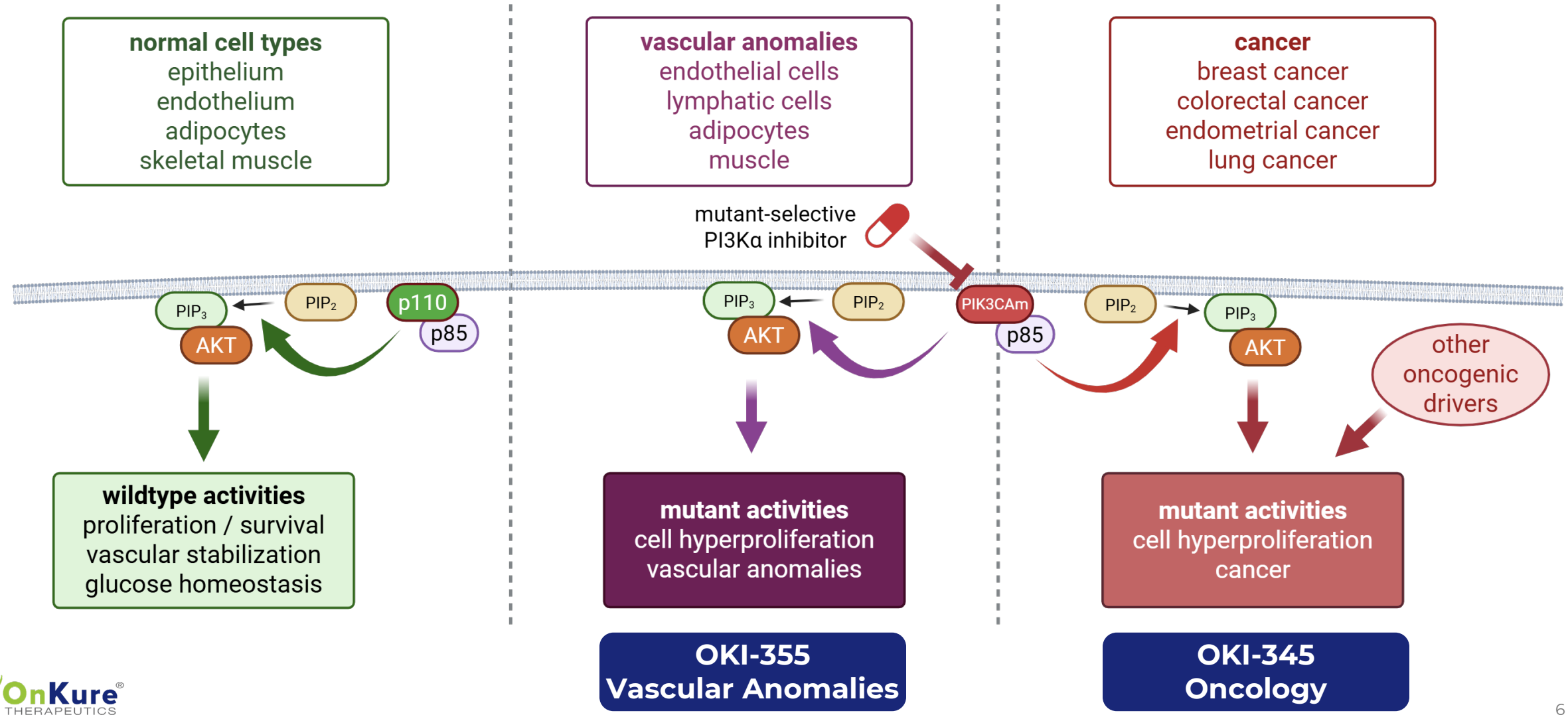
- OKI-355 in Vascular Anomalies
- OKI-345 in Cancer
  - ✓ PI3Kα PAN-mut-selective inhibitors
  - ✓ Best-in-class drug properties
  - ✓ INDs expected 1H 2027

Discovery Programs

- Novel target(s) beyond PI3Kα in Vascular Anomalies

PI3Kα Pathway is Pleiotropic: Central to Normal & Disease Signaling

Disrupted cellular homeostasis due to mutant PI3Kα drives cancers & vascular anomalies



A Differentiated Portfolio

Program	Initial Indication	Discovery	Preclinical	Clinical	Program Status	Next Anticipated Milestone
OKI-355 **PI3Kα^{PAN}** mutant-selective inhibitor	Vascular Anomalies				IND-Enabling Studies Ongoing	IND (1H 2027)
OKI-345 **PI3Kα^{PAN}** mutant-selective inhibitor	Breast Cancer				IND-Enabling Studies Ongoing	IND (1H 2027)
Discovery Target(s) to be announced; systemic and topical	Vascular Anomalies				Active Discovery	To be announced

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Candidate Profile for Potential BIC PI3Kα Pan-Inhibitors

Discovering pan-mutant inhibitors vs. the current landscape

Selectivity

At least 10X cellular selectivity in cell lines with major hotspot mutations in PI3Kα

Efficacy

Potential Best-in-class anti-tumor activity in PI3Kα mutant HR+ BC and Vascular Anomalies models

Safety

Best-in-class avoidance of wild-type PI3Kα and associated toxicities

Coverage

Broad mutant coverage with brain penetration to maximize depth and durability of response

Combinability

Minimal DDI risk enables broad combination use & supports potential use in adjuvant settings

Mutation Resistance

Active against on-target resistance mutants, enabling treatment after PI3Kαi relapse

Diverse IP

Protects assets and disables competition

Candidates

Two development candidates: HR+ Breast Cancer and VA

Comparison of cellular selectivity of OnKure vs. competitor pan-mutant PI3Kα inhibitors

	PI3Kα Mutation		
Compound	**H1047R**	**E545K**	**E542K**
Alpelisib	1x	1x	2x
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All cellular selectivity values were determined by OnKure. Cellular potency for each compound was determined in cell lines with specific PI3Kα mutations shown in parentheses: T47D (H1047R), MCF7 (E545K), BT483 (E542K). Selectivity was derived from the ratio of the potency in a mutant cell line to the wild-type PI3Kα SKBR3 cell line. #OKI-345 is under development in breast cancer; ‡OKI-355 is under development in vascular anomalies

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Benjamin Cravatt, Ph.D.

Characteristics of High-Value Allosteric Pockets

Not all allosteric pockets are equally druggable—successful targets share common features

Desirable Properties

Rare Cryptic State Stabilization

Ligand binding modulates protein activity through allosteric communication networks, leveraging local structural flexibility to enable induced-fit binding and stabilize transient functional conformations that are inaccessible to orthosteric inhibitors

Desirable Outcomes

Accessible Cryptic State

Pocket naturally samples an open conformation, enabling ligand binding without major unfolding

High Druggability

Enclosed geometry with hydrophobic hot spots, H-bonding opportunities, and displaceable waters supports potent small molecules

Target-Specific Pocket Architecture

Enables selective inhibition with reduced off-target activity

Cryptic Allosteric Pockets: A New Path to Better Drugs

Differentiated biology translates into differentiated therapeutics

Traditional Active Site	Cryptic Allosteric Pocket
Conserved across paralogs (*i.e.*, 500+ kinases)	**Often target-specific**
Competition with natural substrate (*i.e.*, ATP)	**Unimpeded access to the cryptic allosteric pocket; higher potency potential**
Resistance-prone	**Orthogonal resistance mechanisms**
Heavily mined target space	**Expands druggable proteome by revealing hidden binding sites**

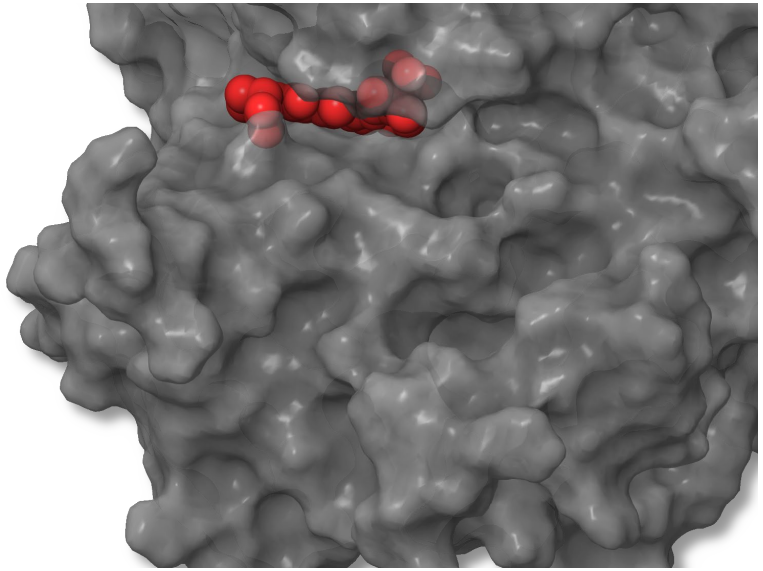
Key Value Drivers

- ✓ Access previously "undruggable" targets
- ✓ Improve selectivity versus orthosteric inhibitors
- ✓ Enable novel mechanisms of action
- ✓ Potential for mutant durable pharmacology
- ✓ Prolonged benefit for patients with resistance to active site drugs
- ✓ Opportunity for best-in-class therapeutics

Cryptic Allostery: A New Path to Better Drugs for PI3K

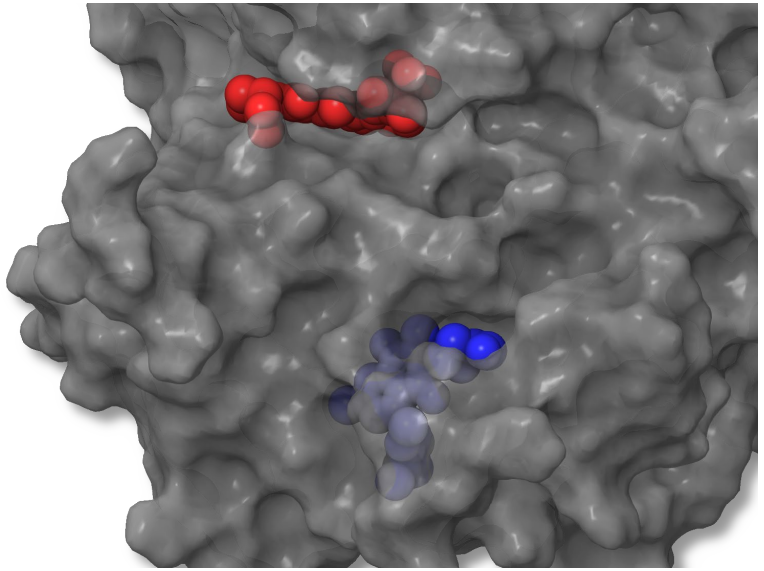
Differentiated biology translates into differentiated therapeutics

Traditional Active Site
Alpelisib: Orthosteric Inhibitor



- Highly conserved binding site
- Competitive orthosteric inhibition
- Limited selectivity; resistance-prone

Cryptic Allosteric Pocket
OKI: Allosteric Inhibitor



- Often target-specific pocket
- Modulates conformational equilibrium
- Higher selectivity; expands druggable proteome

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Note: Illustrative renderings are provided for conceptual purposes only

Allosteric Inhibition Proven in Ph+ CML

SCEMBLIX® (asciminib) establishes clinical validation

Mechanistic Rationale

- Targets a **site other than** the ATP binding pocket
- Enables **high selectivity** vs. conserved kinase domains
- **Avoids direct competition** with high intracellular ATP levels
- Allows **fine-tuned modulation** of protein function
- Reduces risk of **off-target toxicity**
- Creates opportunity for **orthogonal combination strategies**

Clinical Validation

- First-in-class **inhibitor** targeting the ABL myristoyl pocket
- Designed to **overcome** resistance to ATP-competitive TKIs
- Demonstrates activity in **heavily pre-treated CML patients**
- Effective against **T315I & other resistant mutations**
- Improved **safety profile** vs. earlier-generation TKIs
- Validated via **regulatory approval and commercial uptake**

Sequential Innovation Creates Durable Competitive Advantage

Best-in-class franchises emerge from iterative gains in potency, selectivity, resistance coverage, & safety

Franchise	1st Gen First-in-Class	2nd Gen Higher Potency, Enhanced Selectivity	3rd Gen Mutant Target Coverage	4th Gen Improved Therapeutic Index
BCR-ABL	Target validation in CML **imatinib**	Faster, deeper response **dasatinib, nilotinib**	Covers T315I gatekeeper **ponatinib**	Allosteric (STAMP) inhibition **asciminib**
ALK	First-in-class ALK TKI **crizotinib**	CNS-active **alectinib**	Drug resistant mutations **lorlatinib**	**Ongoing Research**
EGFR	First EGFR TKIs **gefitinib, erlotinib**	Irreversible 2G potency **afatinib, dacomitinib**	Covers T790M **osimertinib**	**Ongoing Research**
PI3K	Isoform-selective **idelalisib, alpelisib**	Orthosteric BIC **inavolisib**	Wild-type–sparing Allosteric mutant-selective **(STX-478 & RLY-2608)***	Allosteric pan-mutant selective **OKI-345* & OKI-355***

Sustained value is driven by repeatedly innovating against proven targets — not stopping at the first successful asset

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*Investigational agents.

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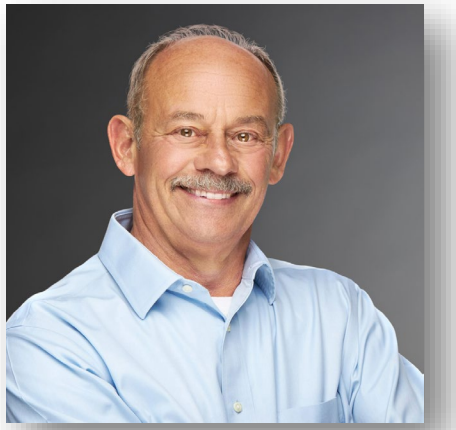


Robert T. Abraham, Ph.D.

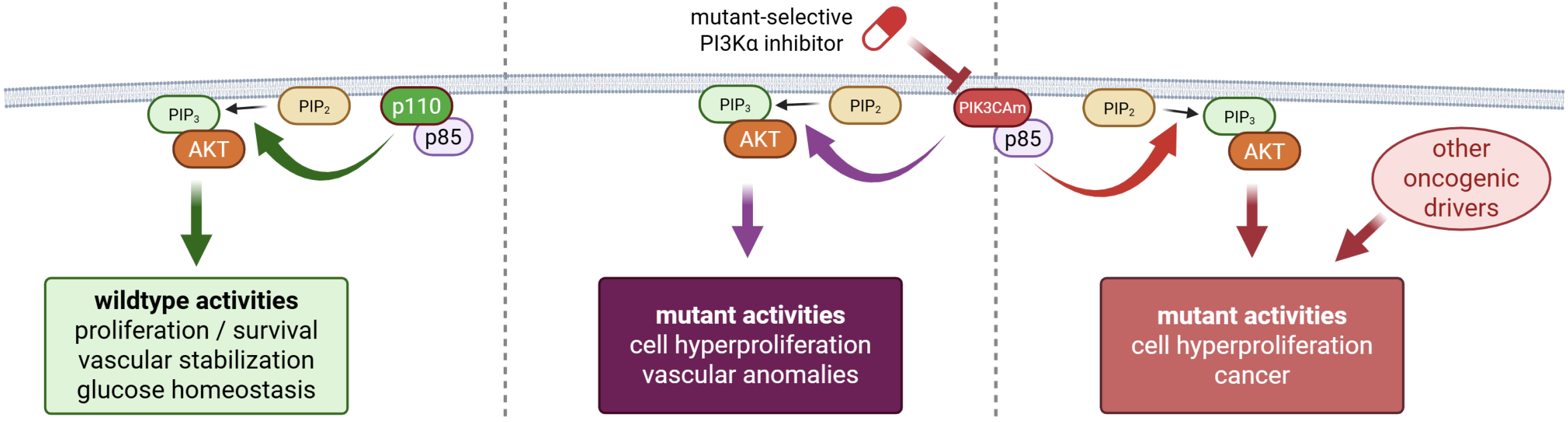
PI3Kα Pathway is Pleiotropic: Central to Normal & Disease Signaling

Disrupted cellular homeostasis due to mutant PI3Kα drives cancers & vascular anomalies

normal cell types
epithelium
endothelium
adipocytes
skeletal muscle

vascular anomalies
endothelial cells
lymphatic cells
adipocytes
muscle

cancer
breast cancer
colorectal cancer
endometrial cancer
lung cancer



wildtype activities
proliferation / survival
vascular stabilization
glucose homeostasis

mutant activities
cell hyperproliferation
vascular anomalies

mutant activities
cell hyperproliferation
cancer

OKI-355
Vascular Anomalies

OKI-345
Oncology

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PI3Kα: From Target Discovery toward Mutant-Selective Medicines

PI3Kα mutations occur in major subset of vascular anomalies and ~15% of all cancers

1983–2000
Target Discovery
- **Studies of a viral oncogene identify PI3Kα as a driver of carcinogenesis**
- Discovery of oncogenic PTEN & PI3Kα mutations further validated the pathway
- PI3K pathway identified as a key regulator of cell growth, metabolism, and survival

2000–2013
Target Validation
- **PI3Kα confirmed as the most clinically relevant oncology target**
- **PI3Kα mutation shown to drive vascular anomalies**
- Early inhibitors (wortmannin, LY294002) demonstrated PI3Kα druggability
- Development shifted toward isoform-selective inhibition

2014–2019
Clinical Validation
- **Alpelisib became the first PI3Kα-selective therapy approved for PI3Kα-mutant solid tumors**

2022
Clinical Approval in PROS
- **Alpelisib approved for PIK3CA-related overgrowth spectrum (PROS), a subset of vascular anomalies**

Next Generation
The Emerging Opportunity
- **Pan-mutant PI3Kα inhibitors**
- Potential to spare wild-type PI3Kα
- Improved therapeutic index & resistance coverage
- Greater combination flexibility

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Challenges in Drugging PI3Kα

Next-generation mutant-selective inhibitors aim to preserve efficacy while reducing wild-type inhibition & metabolic toxicity

Chemistry Challenges

- Development of a pan-mutant inhibitor that targets the ATP binding site (orthosteric) will be extremely challenging
- Discovery & progression of molecules with >10X selectivity to avoid chronically emergent, clinically relevant wild-type derived toxicities

Clinical Challenges

- Use in combination regimens will be required
- Chronic dosing demands improved therapeutic window
  - Wild-type PI3Kα plays key roles in normal cell growth & insulin function
  - On-target toxicities limit dosing: hyperglycemia, rash, diarrhea, stomatitis

The Path Forward

- Mutant-selective inhibition allows dose-intense therapy
- Increased probability of single-agent cytotoxicity
- Sparing of wild-type PI3Kα improves the therapeutic window
- Reduces need for dose reductions or discontinuations due to unacceptable toxicity
- Enables development of 2- and 3-drug combinations to maximize efficacy

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OnKure's Programs

Therapeutic Selectivity & Clinical Performance

Superior selectivity has translated into improved clinical outcomes

Ideal Performance

- Improved target coverage
- Better safety
- Greater combination potential
- Improved patient adherence
- Overall clinical benefit

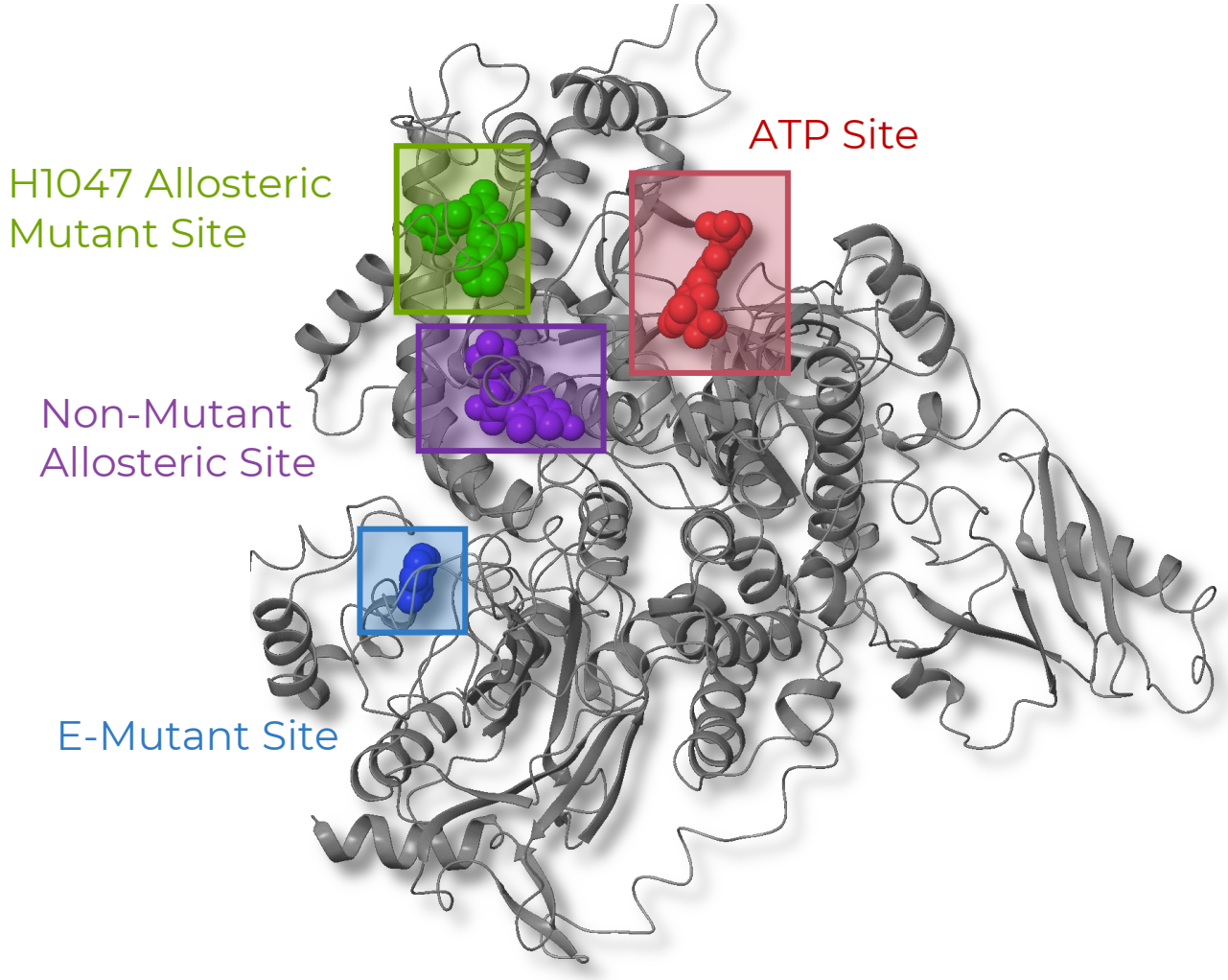
OnKure's Program Goals

- Minimize wild-type PI3Kα inhibition
- Maximize PI3Kα mutant inhibition
- Reduce systemic toxicity
- Establish best-in-class backbone medicine

OnKure's Structure-Based Drug Design Platform Enables Discovery of Allosteric PI3Kα Pan-Mutant Inhibitors

Allosteric pan-inhibitor design

- Targeting regions proximal to PI3Kα mutations:
  - **H1047 allosteric mutant site** (lead)
  - OnKure-discovered **E-mutant site** (proprietary)
- Designed to inhibit both kinase & helical domain mutants (H1047X, E542K, & E545K)
- Targets key regulatory regions driving mutant PI3Kα activation
- Potential to overcome on-target resistance from prior therapies (**orthosteric: alpelisib and inavolisib; non-mutant allosteric: STX-478 and RLY-2608**)



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Discovering pan-mutant inhibitors vs. the current landscape

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Selectivity Provides Deeper Responses when Dosed to MTD

A wider therapeutic window allows for greater mutant target coverage

Cellular Selectivity vs. SK-BR-3 WT

		PI3Kα Mutation		
selectivity range	**compound**	**H1047R**	**E545K**	**E542K**
low	alpelisib	1x	1x	2x
	STX-478	6x	2x	3x
	RLY-2608	5x	2x	2x
>10x	**OKI-345**	**58x**	**18x**	**10x**
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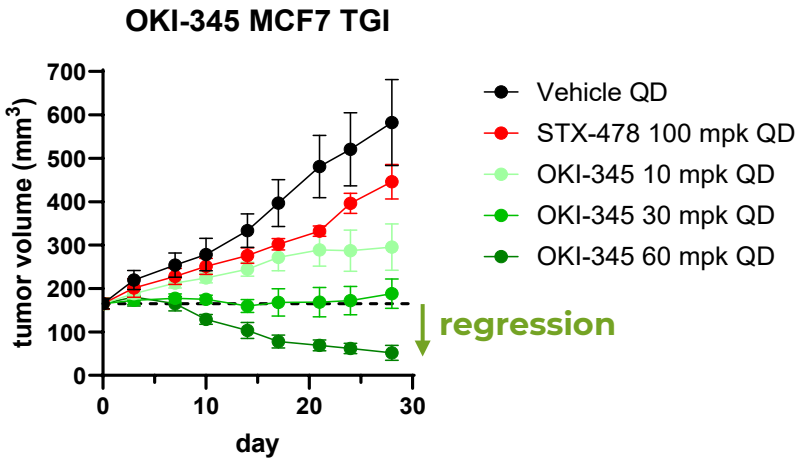
OKI-345 Drives Regressions in MCF7 Helical (E545K) Domain Mutant Xenograft Model



OKI-345 Greater Selectivity Leads to Superior Target Coverage and Efficacy over the Competition

The MCF-7 xenograft is ER+/PR+, HER2- and PI3Kα **helical-domain hotspot mutant (E545K)** breast cancer. STX-478 was tested at the published dose in mice (Buckbinder et al., 2023)

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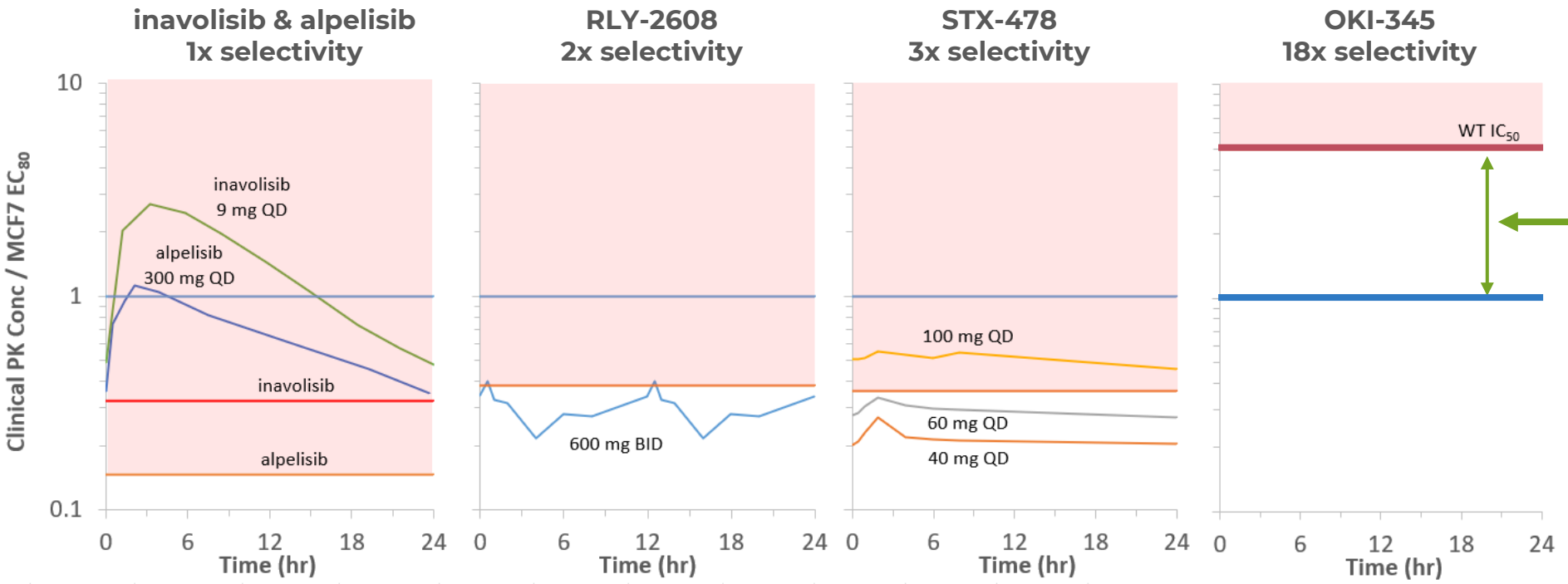
OnKure's Thesis: Best-in-Class Selectivity Enables Greater Target Coverage to Unlock an Expanded Therapeutic Index



Greater **separation** between the red & blue lines reflects an **expanded** therapeutic window

Clinical[1] C_p / MCF7 EC_{80} plots demonstrate that OKI-345 is expected to engage mutant PI3Kα well below the WT IC_{50}, whereas the competitors will risk hyperglycemia/hyperinsulinemia

- Values > 1 (blue line) indicate clinically relevant target inhibition
- Values > WT PI3Kα EC_{50} (pink shaded area) indicate risk of hyperglycemia

[1]EC80 is recognized as a clinically relevant threshold for efficacy

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Q&A

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Selectivity Matters and Pan-Mutant Allosteric Inhibition Delivers

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