OnKure Therapeutics

August 2026

Legends

This presentation contains forward-looking statements that involve substantial risks and uncertainties of OnKure Therapeutics, Inc. ("OnKure" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, 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; the potential of PI3KαMUT inhibitor-based therapies; OnKure's ability to advance additional programs; the expected milestones and timing of such milestones, details on the pan-mutant program and the timing of the submission of the IND applications for OKI 345 and OKI 355; the completion and expected timing of the closing and gross proceeds received by OnKure in the private placement; OnKure's expected use of net proceeds from the private placement, OnKure's expected cash runway, OnKure's ability to leverage insights from the PIKture-01 trial and statements regarding OnKure's financial position, including its cash runway. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," " expect," "may," "plan," "potentially," "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our 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: the risk that the conditions to the closing of the private placement are not satisfied; 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 our 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; the ability to attract, hire, and retain highly skilled executive officers and employees; the ability of OnKure to protect its intellectual property and proprietary technologies; the scope of any patent protection OnKure obtains or the loss of any of OnKure's patent protection; 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 other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in documents that OnKure files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our 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 we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

OnKure is Developing a Differentiated Portfolio

OnKure Therapeutics

- **Developing PI3Kα PAN-mutant inhibitors** with the highest known selectivity on helical and kinase mutations
- Two distinct candidates designed for **Vascular Anomalies & Cancer**
- Experienced R&D team to support portfolio expansion in vascular anomalies beyond PI3Kα
- **$176M in cash and marketable securities** as of June 30, 2026, expected to fund operations into 2029

Pipeline

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

Led by a Team with Proven Experience

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President and
Chief Executive Officer

ARRAY BIOPHARMA · BEND RESEARCH · Pfizer

Samuel Agresta, M.D., MPH
Chief Medical Officer

Infinity · agios · Genentech A Member of the Roche Group

Jason Leverone
Chief Financial Officer

miRagen · Replidyne · ARTHUR ANDERSEN

Dylan Hartley, Ph.D.
Chief Scientific Officer

Pfizer · ARRAY BIOPHARMA · MERCK · Genentech A Member of the Roche Group

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VP of Pharmaceutical
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Pfizer · BEND RESEARCH

Qian Zhao, Ph.D.
VP and Distinguished Fellow

NOVARTIS · Pfizer · ARRAY BIOPHARMA

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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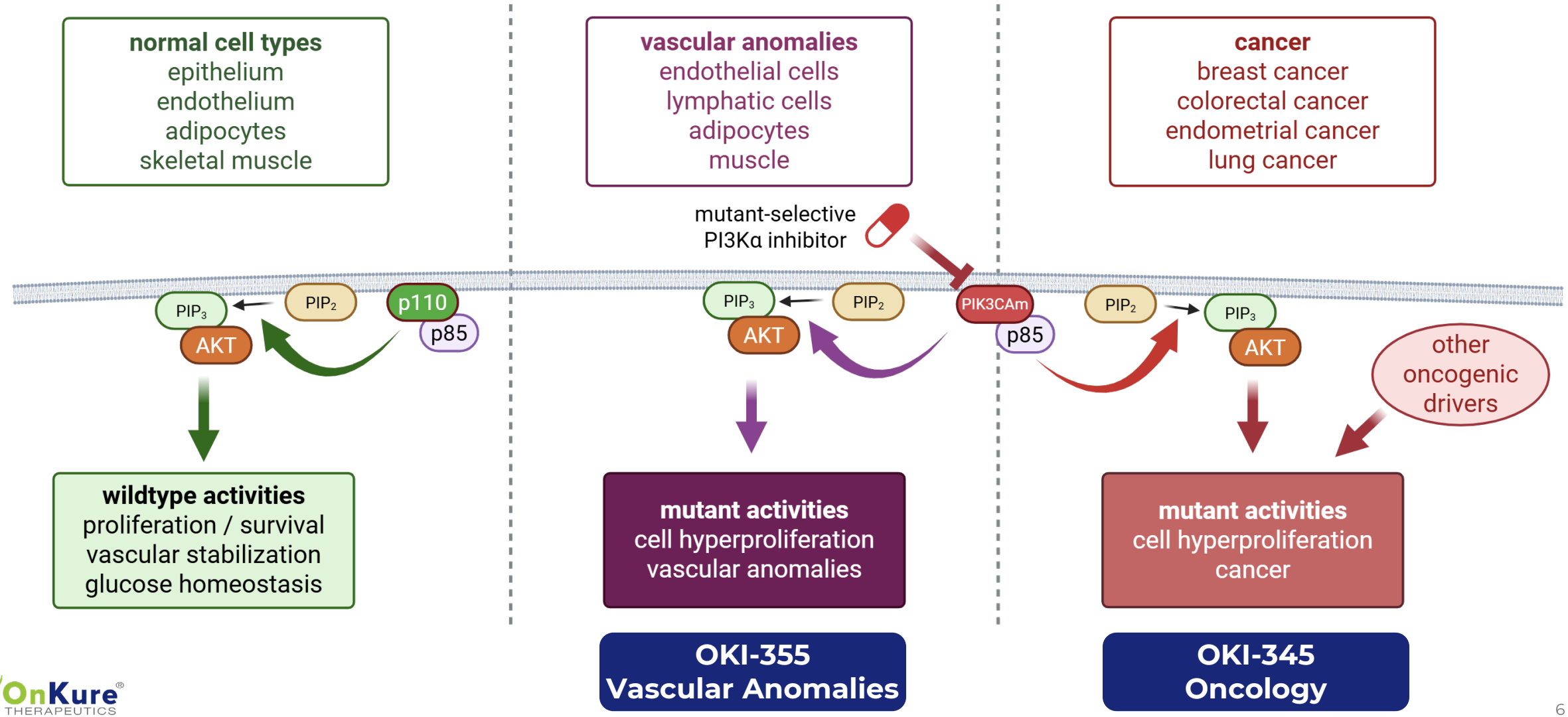
PI3Kα Pathway is Pleiotropic: Central to Normal & Disease Signaling

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



Sequential Innovation Creates Durable Competitive Advantage

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

Targeted Therapies	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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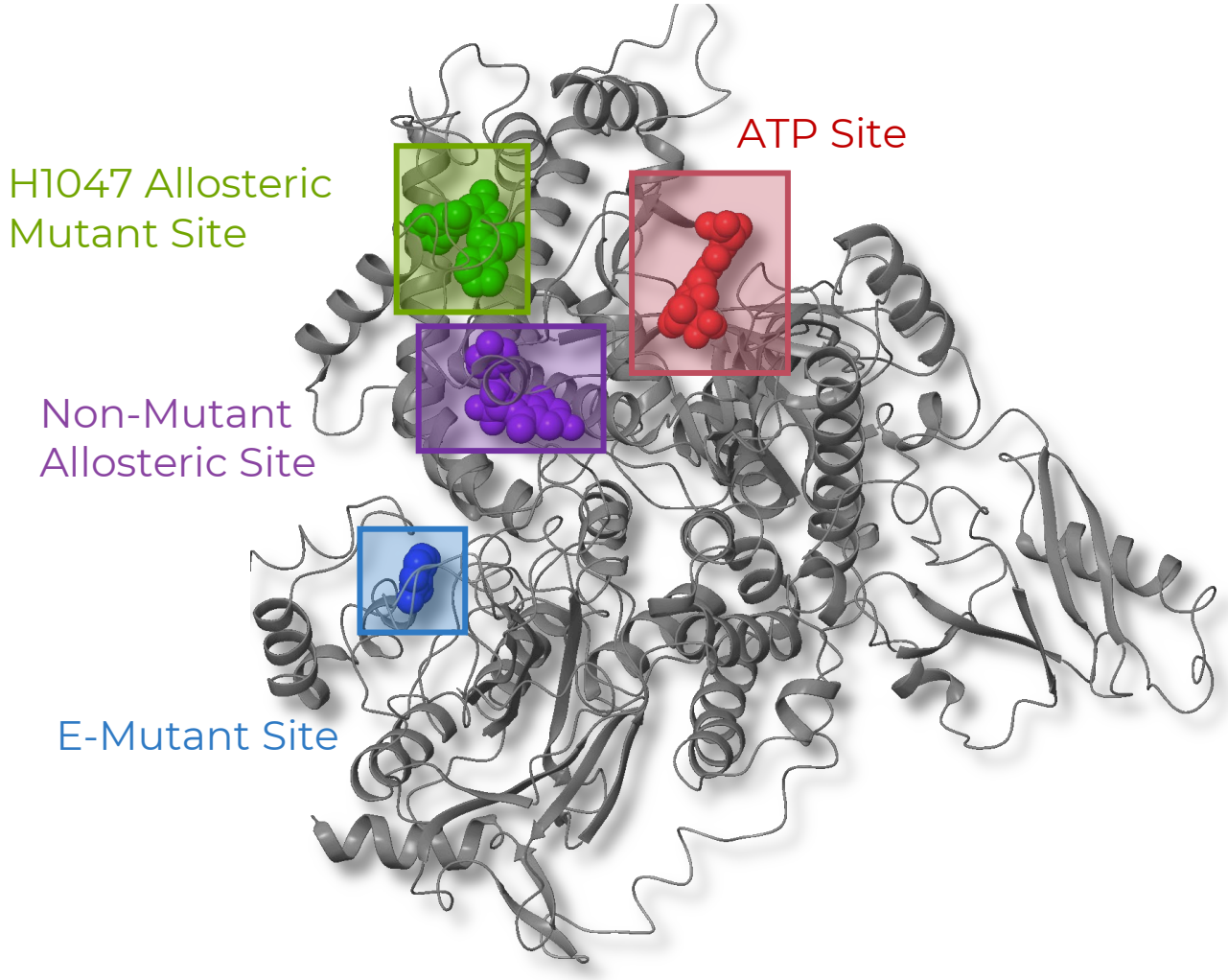
*Investigational agents.

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, inavolisib; non-mutant allosteric: STX-478, RLY-2608**)



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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
STX-478	6x	2x	3x
RLY-2608	5x	2x	2x
OKI-345#	**58x**	**18x**	**10x**
OKI-355‡	**106x**	**24x**	**10x**

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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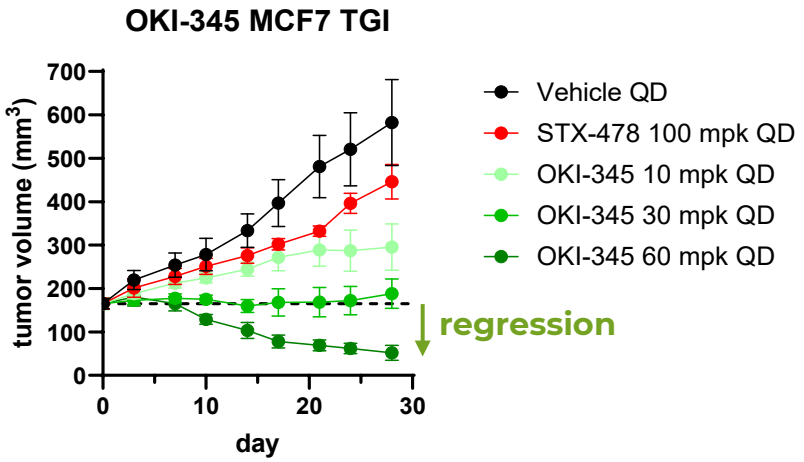
Selectivity Provides Deeper Responses when Dosed to MTD

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**
	OKI-355	106x	24x	10x

OKI-345 Drives Regressions in MCF7 Helical (E545K) Domain Mutant Xenograft Model

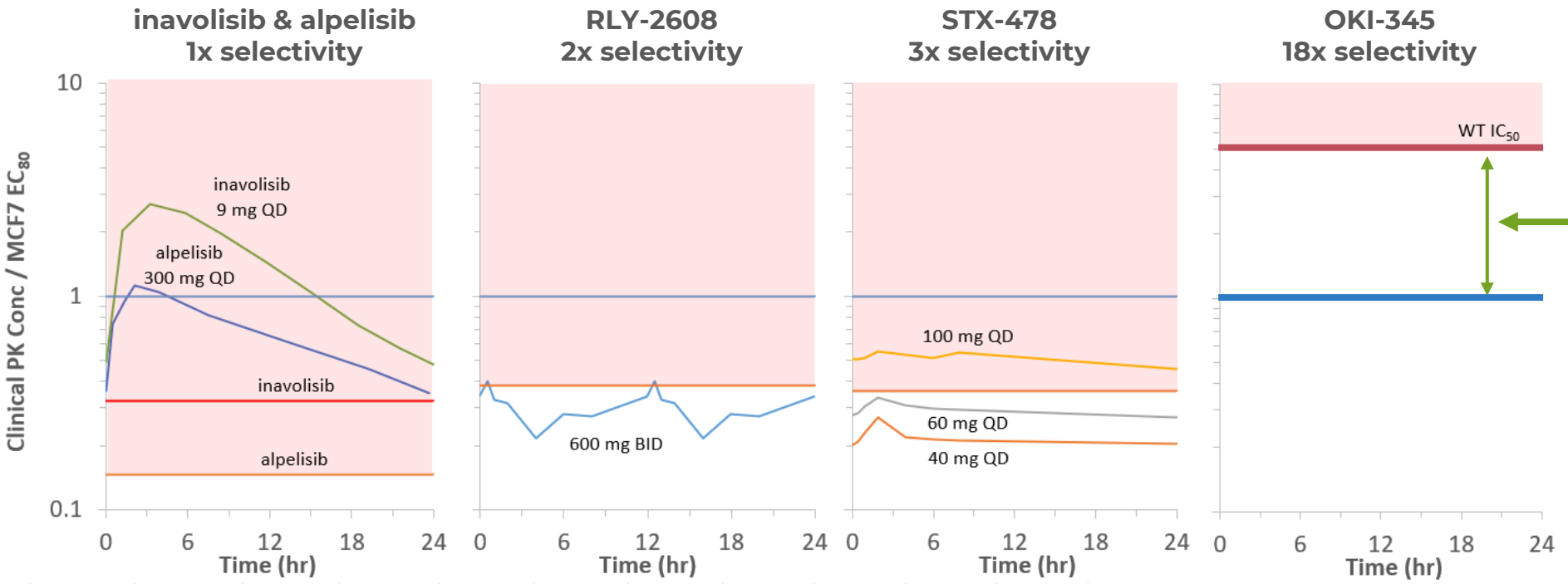


OKI-345 Greater Selectivity Leads to Superior Target Coverage and Efficacy over the Competition

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)

OnKure® THERAPEUTICS

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 (E545K) 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

Vascular Anomalies Patients Deserve Precision Therapies

Vascular anomalies are monogenic targetable diseases that cause measurable functional impairment and burden

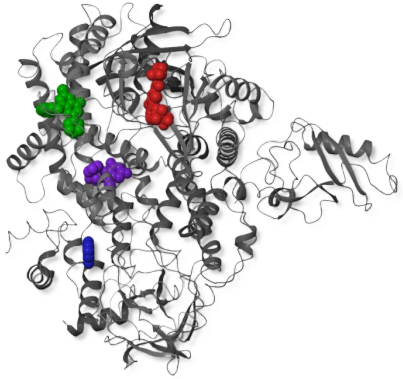
~86K

Target PI3KCAm Patient Population in the US

Non-selective PI3Kα drugs are of limited use due to wild type toxicities

Mutant-selective PI3Kα drugs could transform standard of care and offer a lifetime of benefit

PI3Kα is a **clinically validated Vascular Anomalies target**



OKI-355 – PI3Kα pan-mutant selective candidate; IND 1H 2027

Our **approach restores cellular homeostasis** by selectively targeting mutant PI3Kα

OnKure's edge

Track record	R&D team experienced in rare diseases
IP	Ability to leverage existing OnKure IP
Target	Leading expertise in PI3Kα drug discovery
Clinical	Novel biomarkers + meaningful endpoints

Note: prevalence based market benchmarks and internal analysis

Available Therapies for Vascular Anomalies are Inadequate

Alpelisib & Rapamycin Validate PI3Kα as Target, but Wildtype Toxicity Limits Activity

ALPELISIB (VIJOICE)

- **Clinical efficacy limited by tolerably**. EPIK-P2 confirmatory study showed limited efficacy (ORR: 11% adults, 9% peds)[1] at lower doses to mitigate toxicity
- Ongoing EPIK-P4 study attempts to re-capture efficacy in PROS, again **pushing higher doses**
- EPIK-L1 explores expansion in LM despite a **therapeutic window** which appears to be **constrained by wild-type inhibition**
- Validates the role of PI3Kα inhibition, but its therapeutic profile underscores the shortcomings of non-selective approaches – **unmet need remains despite target validation**

SIROLIMUS (RAPAMYCIN)

- **Not approved** in any subset of vascular malformations; off-label use
- Non-selective profile associated with **challenging toxicity profile including immunosuppression**
- Requires frequent **monitoring with blood tests** for dose control and safety surveillance:
  - **Blood** → myelosuppression (anemia, thrombocytopenia, leukopenia)
  - **Lipids** → hypercholesterolemia/ hypertriglyceridemia
  - **Kidneys and Liver** → creatinine changes, proteinuria, hepatic effects

[1]Canaud, G. et al. Epik-P2: A Phase 2 Study of Alpelisib (ALP) in Pediatric and Adult Patients (pts) with PIK3CA-Related Overgrowth Spectrum (PROS). Blood 144, 5512–5512 (2024)

Vascular Anomalies: 86,000 Target U.S. Patient Population

Multi-Billion-Dollar Opportunity, Significant Patient Burden, and Inadequate Treatment Options

Vascular Anomalies

Prevalence (U.S.)[1]	Approved Therapies	Disease Presentation
Venous Malformations **~ 22,000 PIK3CAm**	**None**	**Neurologic** Seizures, cognitive delays **Infection** Cellulitis, bacteremia **Organ abnormalities** Pulmonary, cardiac, renal, hepatic, GI **Functional impairment** Pain, muscular, orthopedic, soft tissue overgrowth **Lymphatic** Lymphedema, lesions, chylous effusion/ascites **Coagulopathies** Hemorrhage, thrombophilia **Psychologic** Anxiety, depression
Lymphatic Malformations **~49,000 PIK3CAm**	**None**	
PIK3CA Related Overgrowth Spectrum (PROS) **~ 15,000 PIK3CAm**	**Alpelisib** (approved in subset of PROS with severe disease manifestations)	

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[1]prevalence and market size estimates based on market benchmarks and internal analysis

PIK3CA Mutated MBC Represents A Major Market Opportunity

A Multi-Billion-Dollar Market Opportunity

~38% of breast cancers harbor PIK3CA mutations[1]

Patient Population	Target Population (U.S. Patient Incidence)[2]	Total Addressable Market (TAM)[2]
1L HR+/HER2- mBC Estrogen Sensitive	**10,900**	**~$7-9B**
1L HR+/HER2- mBC Estrogen Resistant	**5,300**	**~$2-3B**
HR+/HER2- mBC 2nd-3rd Line	**9,750**	**~$2-3B**

OnKure's Differentiation

Best-in-Class
Safety and Tolerability

Enable Combinability
with Backbone Therapies
Across All Lines of Therapy

Activity and Tolerability Drive
Extended Duration of Therapy

[1]third party source. [2] Total Addressable Market (TAM) and target patient population based on market benchmarks and internal analysis

OnKure® THERAPEUTICS

Financial Overview

Stock Symbol	NASDAQ: OKUR
Cash	**$176 million** cash, cash equivalents, and marketable securities as of June 30, 2026
Cash Runway	Cash, cash equivalents, and marketable securities as of June 30, 2026 **expected to fund operations into 2029**
Common Stock	**40.5 million shares** of common stock plus pre-funded warrants to purchase **9.4 million shares** of common stock outstanding as of June 30, 2026

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