OnKure® THERAPEUTICS

Corporate Overview

December 2024

Legends

Forward-Looking Statements

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 and plans regarding, OnKure's product candidates and programs, including OKI-219; the potential of PI3Kα^{MUT} inhibitor-based therapies; OnKure's ability to advance additional programs; planned expansion combination arms; the expected milestones and timing of such milestones, including for OKI-219 and its discovery programs; 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," "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: OnKure's limited operating history; the significant net losses incurred since inception; the ability to raise additional capital to finance operations; 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.

Investment Highlights

PI3Kα is the most frequently mutated oncogene

Highly selective, targeted therapies offer the potential for significant improvement in patient outcomes

OnKure is developing a best-in-class portfolio of highly mutant-selective PI3Kα inhibitors **designed to preserve wild-type PI3Kα while effectively targeting the majority of PI3Kα-mutated cancers**

- OKI-219 is a PI3Kα^{H1047R} mutant selective inhibitor being evaluated in a Phase 1 trial as a monotherapy and in combination with other agents in breast cancer
- Preclinical pipeline includes: PI3Kα ^{PAN} and PI3Kα $^{E542K, E545K}$ programs
- Cash and investments expected to provide funding through multiple clinical milestones and runway into Q4 2026

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Leadership Team with Proven Experience

Nicholas Saccomano, Ph.D.
President and
Chief Executive Officer

ARRAY BIOPHARMA · BEND RESEARCH · Pfizer

Jason Leverone
Chief Financial Officer

miRagen · Replidyne · ARTHUR ANDERSEN

James Blake, Ph.D.
SVP of Computational
Drug Discovery

Pfizer · ARRAY BIOPHARMA

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

Infinity · agios · Genentech A Member of the Roche Group

Rogan Nunn, J.D.
General Counsel and
Secretary

ADC THERAPEUTICS · ARRAY BIOPHARMA · Skadden

Robbie Alton, Pharm
VP of Clinical Operations

Halozyme · Denovo Biopharma

Dylan Hartley, Ph.D.
Chief Scientific Officer

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

Mark L. Boys, Ph.D.
SVP of Discovery
Chemistry

gsk · Pfizer · ARRAY BIOPHARMA

Kevin S. Litwiler, Ph.D.
SVP of DMPK and Clinical
Pharmacology

Pfizer · ARRAY BIOPHARMA

Duncan Walker, Ph.D.
Chief Development Officer

KYMERA · forma THERAPEUTICS · ARRAY BIOPHARMA

Ann Howell, Pharm.D.
VP of Regulatory Affairs

Forest Laboratories, Inc. · novo nordisk®

Jim Wong, Ph.D.
VP of Biological Sciences

OncoMed PHARMACEUTICALS · Pfizer · Genentech A Member of the Roche Group · ARRAY BIOPHARMA

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Mutant-Selective PI3Kα Inhibitors

Targeting the Majority of PI3Kα-mutated Cancers While Preserving Wild-type PI3Kα

PI3Kα mutant specific portfolio

Program/Target	Indication(s)	Discovery	Preclinical	Clinical	Current Status	Next Anticipated Milestone
OKI-219 **PI3Kα^{H1047R}** mutant-selective inhibitor	Breast cancer & solid tumors			PIKture-01 Trial	Phase 1 enrolling	Data Update (2H 2025)
OKI-TBD **PI3Kα^{PAN}** mutant-selective inhibitor	Solid tumors & breast cancer				Candidate selection	Select candidate (1H 2025)
OKI-TBD **PI3Kα E542K, E545K** mutant-selective inhibitor	Solid tumors & breast cancer				Active discovery	Select candidate (2026)

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PI3Kα: The Most Commonly Mutated Oncogene

A Need for Highly Selective Mutant Inhibitors that Improve Efficacy and Safety

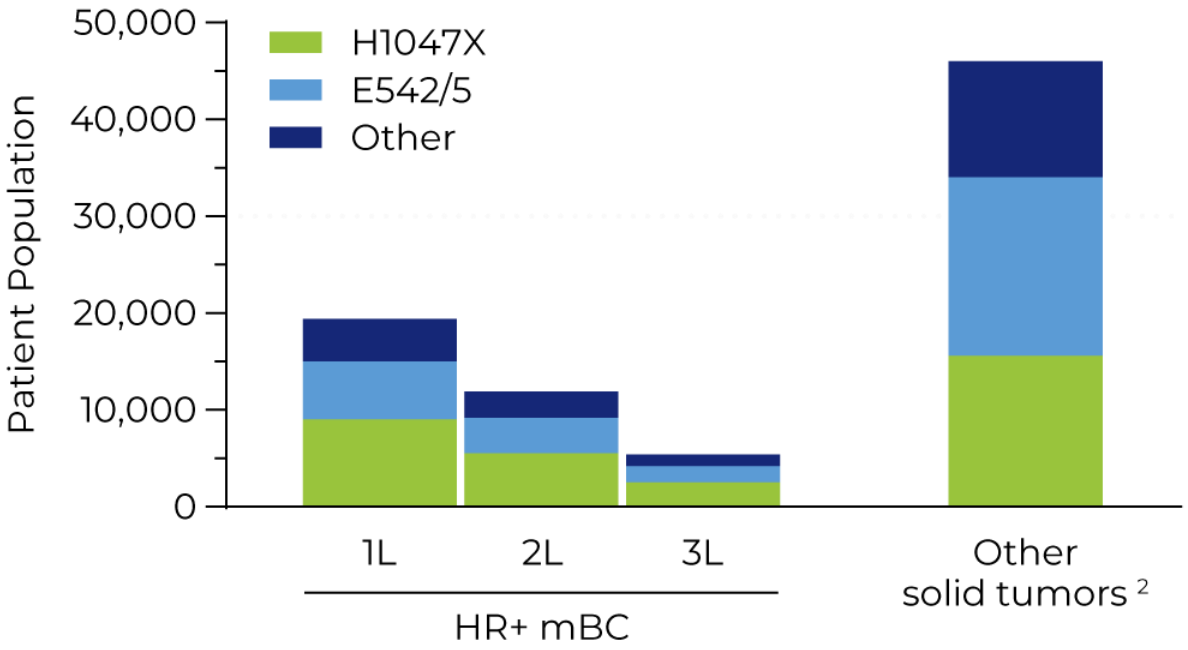
PI3Kα: A validated target in HR+ MBC

- Three approved drugs
  (alpelisib, capivasertib, and inavolisib)
- However, on-target toxicity of inhibiting wild type significantly limits dosing and decreases quality of life[5,6]

OnKure is developing mutant-selective inhibitors designed to preserve wild-type

- **PI3Kα^{H1047R*}** OKI-219, in Phase 1
- **PI3Kα ^{PAN}** candidate selection 1H 2025
- **PI3Kα $^{E542K, E545K}$** active discovery

US Patient Population[1]

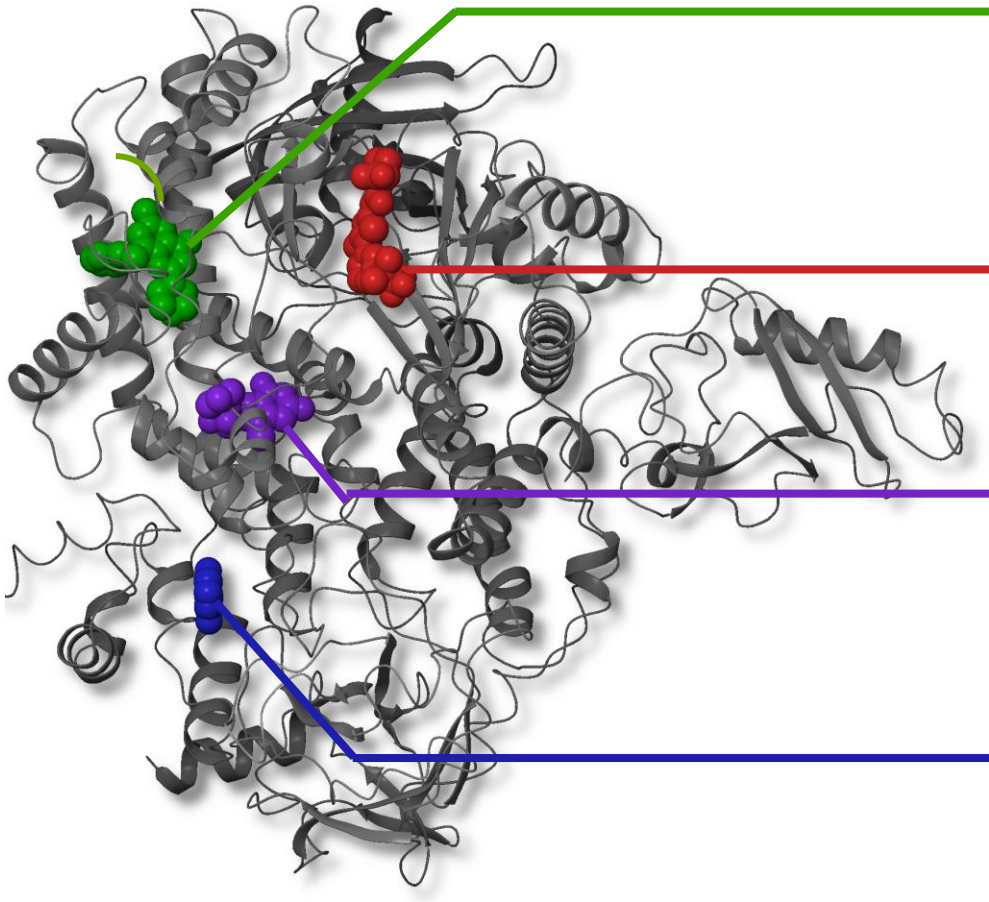


*PI3Kα^{H1047R} is the most common hot spot mutation[3] present in ~15% of breast and ~4% of all human cancers[4]

1. Data from Tumor portal; ACS Cancer Facts and Figures; Sanger COSMIC database and cBioPortal and Independent market analysis.
2. Estimate of Salvage Therapy patients based on cancer Deaths (US Patients; ACS cancer facts and figures, Globecan)
3. 1 Kandoth, C., McLellan, M., Vandin, F. et al. Nature 502, 333–339 (2013); http://www.tumorportal.org/#gene
4. https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=PIK3CA#references
5. Fritsch et al Mol Cancer Ther; 13(5) May 2014, 6. Juric et al, JCO, 36 (13), 2018

Next-Gen PI3Kα Mutant-Targeting Landscape

Mutant-Selectivity is Necessary to Drive Improved Efficacy and Safety



PI3Kα^{H1047R} Inhibitors

- Phase 1: OKI-219, previously LOXO-783
- Highly selective; wide therap. index preclinically

ATP Site Competitive Inhibitors

- Alpelisib approved
- Inavolisib approved

Non-Mutation Site Allosteric Inhibitors

- Phase 1: Relay & Scorpion
- Single-digit selectivity
- Initial proof of concept data

PI3Kα$^{E\text{-}mutant}$ Inhibitors

- E-mutation-specific
- No known clinical trials
- OnKure preclinical program

Reported Cell-Based Selectivity for PI3Kα^{H1047R} vs PI3Kα^{WT}

Compound	H1047R
Alpelisib[1]	1
STX-478[1]	8.8
RLY-2608[2]	3.8
OKI-219[3]	**~100**

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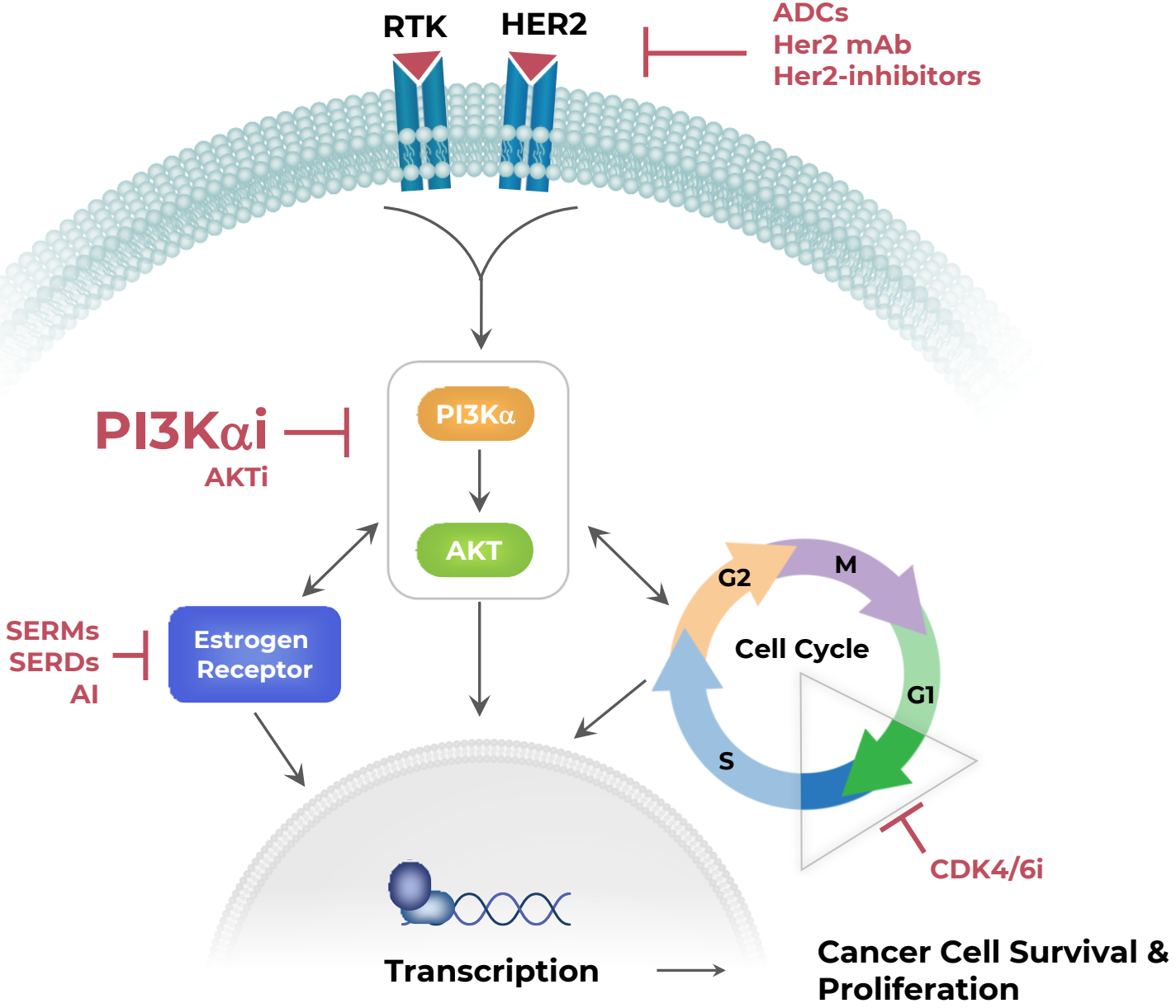
[1] Buckbinder et al Cancer Discov 2023;13:2432–47 [2] Varkaris et al Cancer Discov 2024;14:1–18 [3] OnKure internal data

PI3Kα^{MUT} Inhibitors:

Potential Backbone Therapy in Combination with Approved Agents in Breast Cancer



SERM: Selective Estrogen Receptor Modulator
SERD: Selective Estrogen Receptor Degrader
AI: Aromatase Inhibitor
ADC: Antibody Drug Conjugate

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PI3Kα Mutated HR+ MBC: A Major Market Opportunity

PI3Kα^{H1047R} Mutated HR+ Metastatic Breast Cancer: Significant Unmet Need

HR+ accounts for ~70% of all BrCa cases[1]

	Current & Near-Term Treatments	Treatable US Population[2]
Adjuvant	**NONE**	**~25K**
1st Line	**INAVOLISIB** + palbociclib + fulvestrant	**~9K**
2nd Line	**ALPELISIB** + fulvestrant **CAPIVASERTIB** + fulvestrant	**~5.5K**

[1]https://seer.cancer.gov/statfacts/html/breast-subtypes.html
[2]Third party research

OKI-219: Targeted for Development Across Adjuvant & MBC

Properties of OKI-219 suggest potential to demonstrate safety and efficacy in **both adjuvant and metastatic settings**

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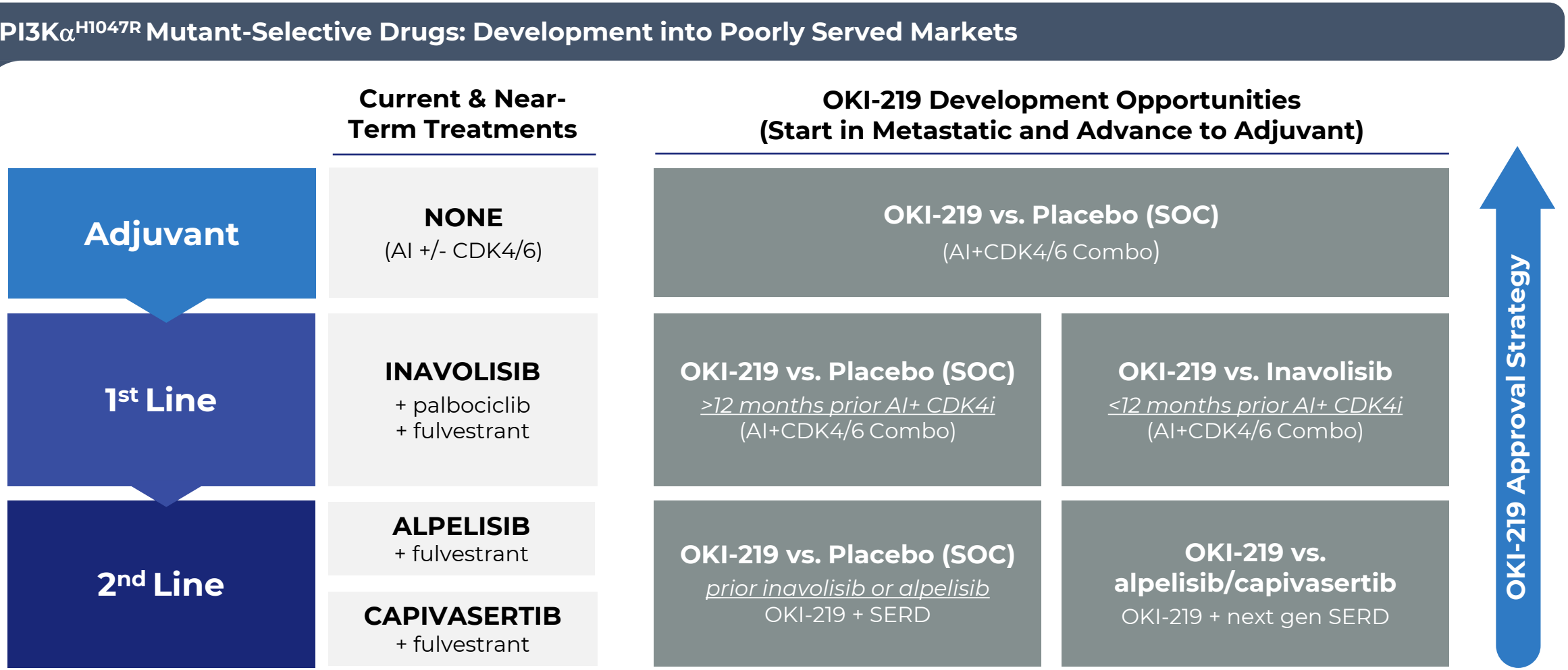
OKI-219: Multiple Development Opportunities

The Potential to Reach Across Multiple Lines of Therapy

PI3Kα^{H1047R} Mutant-Selective Drugs: Development into Poorly Served Markets



SOC: Standard of Care

Preclinical Safety and Efficacy Profile Shows High Potential

Selectivity/ Efficacy

OKI-219 highly mutant-selective (~100X for H1047R vs. wt) inhibition leads to superior efficacy

Potential for superior target coverage at accessible tolerated doses

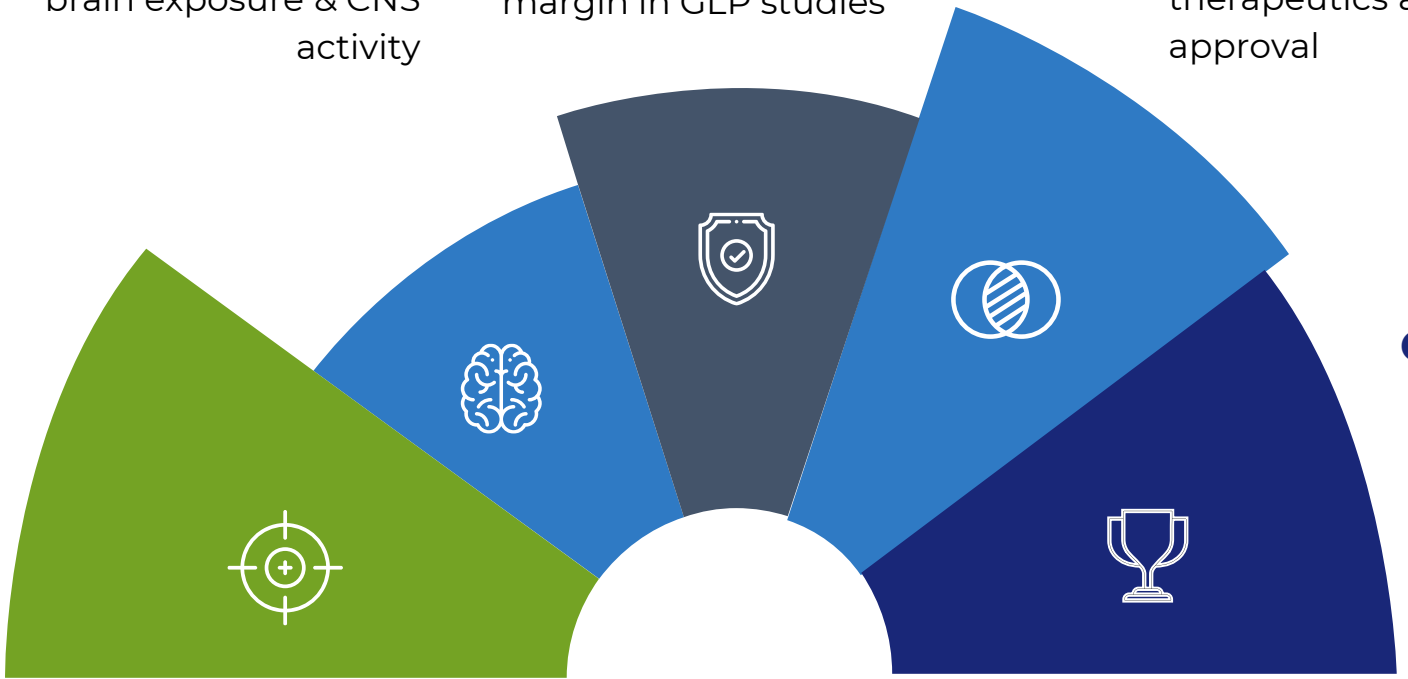
Brain Penetration

Demonstrated excellent brain exposure & CNS activity

Safety

OKI-219 has been well-tolerated with lack of glycemic effects

Wide therapeutic margin in GLP studies



Combinability

OKI-219 shows preclinical efficacy at low doses in single-agent, SOC combinations and with novel therapeutics approaching approval

Overcomes Resistance

Overcomes PI3Kα^{H1047R} driven resistance in combination with tucatinib or trastuzumab

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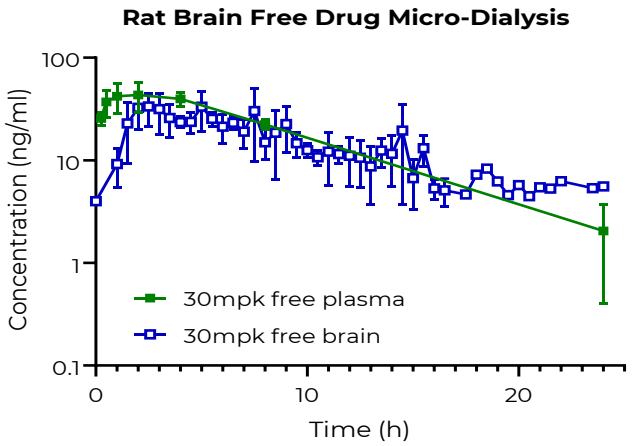
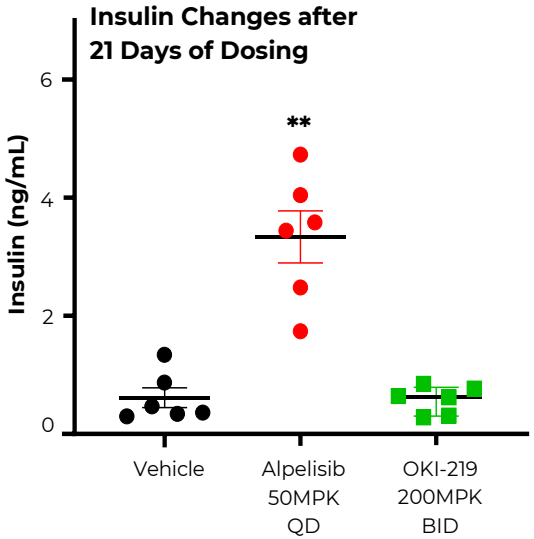
Preclinical Safety and Efficacy Profile Shows High Potential

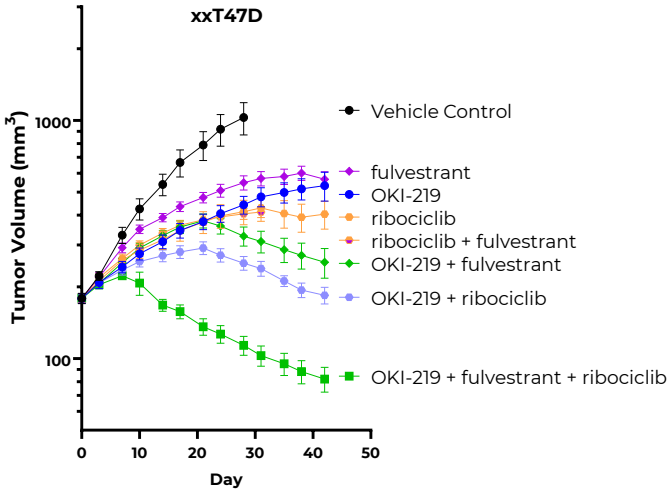
Brain Penetration



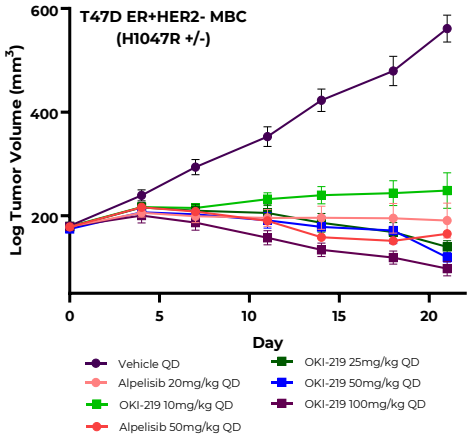
Safety



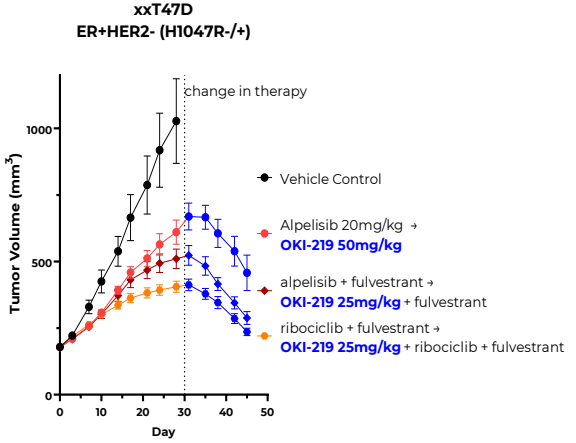
Combinability



Selectivity/ Efficacy

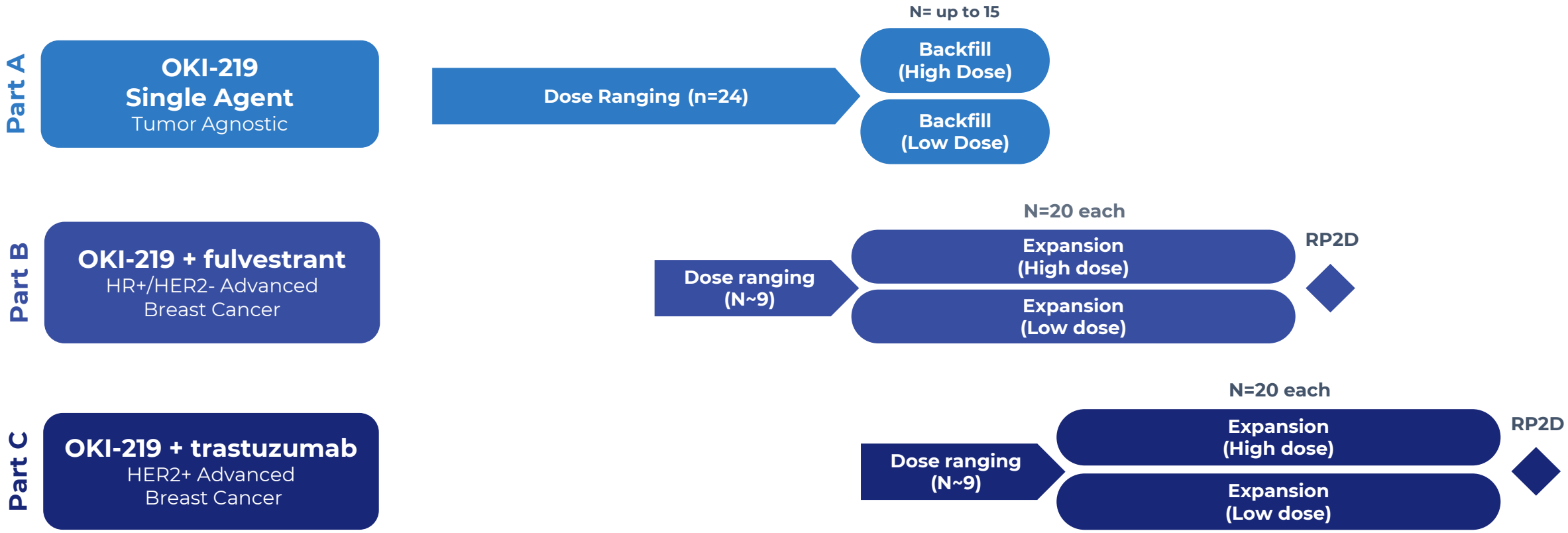


Overcomes Resistance



PIKture-01 Phase 1 Clinical Trial

An Open-Label, Multicenter, Dose-Escalation First-in-Human Trial of OKI-219



Additional expansion combination arms are being planned

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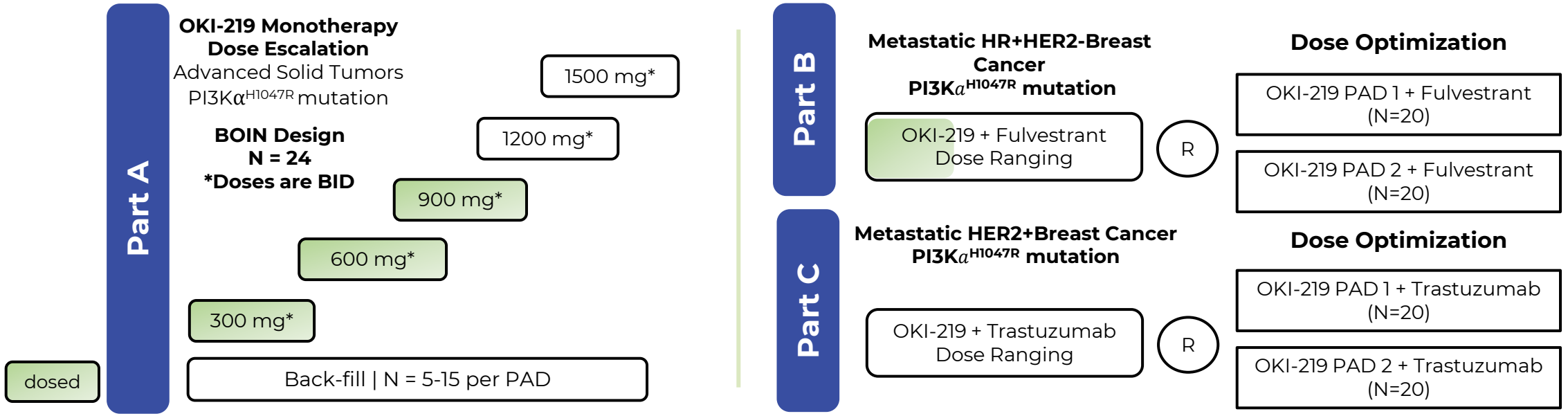
RP2D: Recommended Phase 2 Dose

PIKture-01 Study Design

As of October 28, 2024



Key Eligibility Criteria:

- PI3Kα^{H1047R} advanced solid tumors who received prior SOC
- Prior PIK3 inhibitors of any kind allowed
- Treated or untreated asymptomatic brain metastasis allowed
- HbA1C < 8% allowed

Key Endpoints:

- Safety and tolerability
- PK, PD, RP2D incorporating Project Optimus[1]
- Anti-tumor activity assessed by ORR by RECIST v1.1, DOR, PFS
- Patient reported outcomes via EORTC QLQ-C30 score during dose optimization only

BOIN: Bayesian Optimal Interval Design; DOR: Duration of Response; ORR: Objective Response Rate; PFS: Progression Free Survival; PAD: Pharmacologically Active Dose; PD: Pharmacodynamics, PK: Pharmacokinetics; R: Randomization; RP2D: Recommended Phase 2 Dose; SOC: Standard of Care. NCT:06239467

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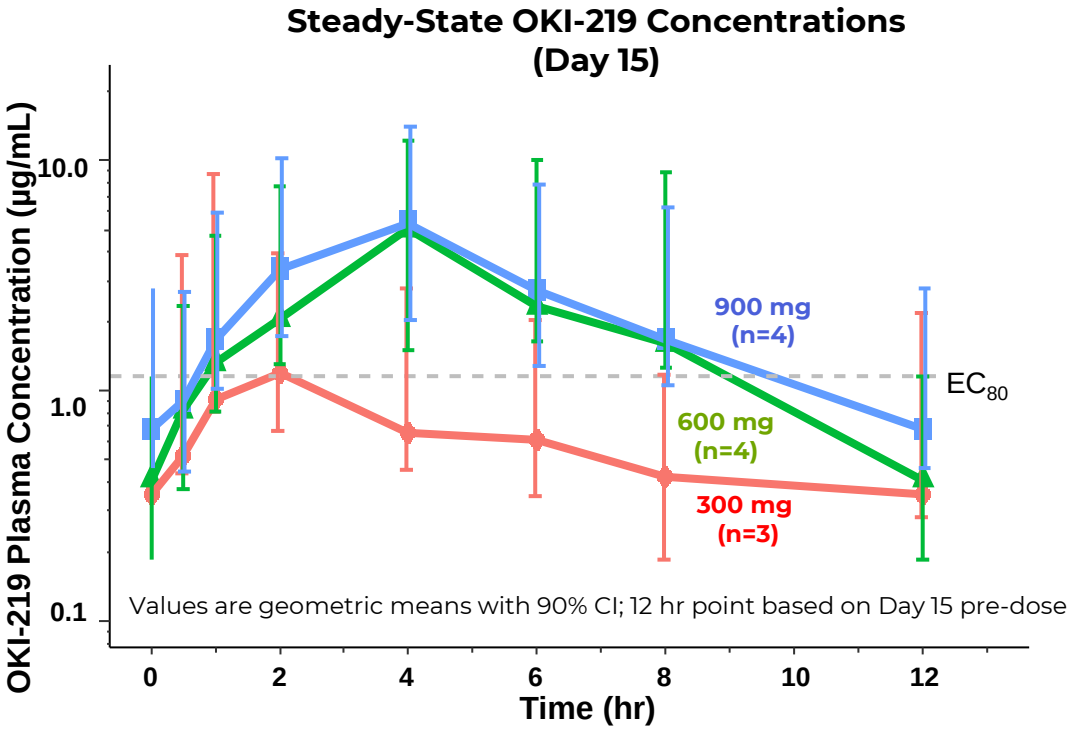
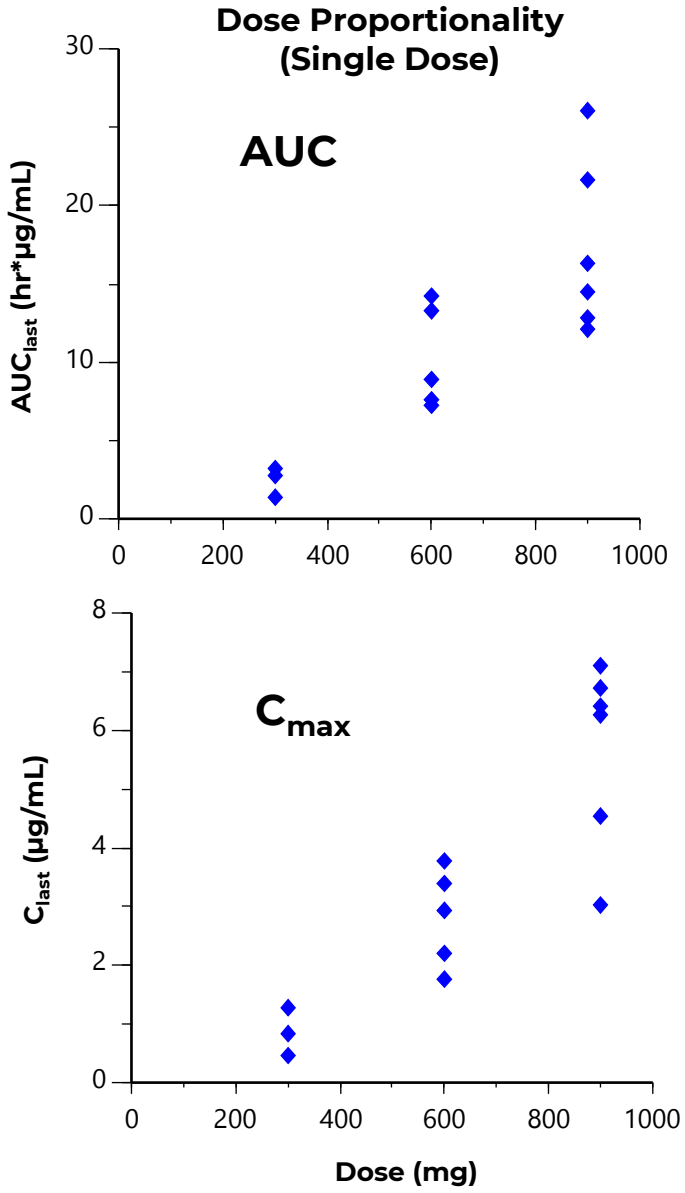
1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases

Pharmacokinetics: Highly Developable Candidate Profile





Steady-State OKI-219 PK Estimates

Parameter	300 mg BID	600 mg BID	900 mg BID
T_{max} (hr)	2.0	4.0	3.0
C_{max} (µg/mL)	1.47	5.33	5.94
AUC_{tau} (hr*µg/mL)	7.55	26.0	30.5

Values are geometric means except for T_{max} which is median

CI: Confidence Interval

- Steady-state exposures (900 mg BID) show near-continuous coverage
- Single dose, dose proportional exposure (C_{max}, AUC)
- OKI-219 is rapidly absorbed with modest accumulation

Only Grade 1 TRAEs Observed Across All Dose Levels

No Hyperglycemia, Stomatitis, or Rash Observed at Any Dose

	300 mg BID n = 3	600 mg BID n = 8	900 mg BID n = 6	ALL Pts n=17
Preferred Term	**Grade 1**	**Grade 1**	**Grade 1**	**Grade 1**
Diarrhoea	0 (0%)	3 (38%)	1 (17%)	4 (24%)
Nausea	0 (0%)	1 (13%)	1 (17%)	2 (12%)
Pruritus	1 (33%)	1 (13%)	0 (0%)	2 (12%)
Anaemia	0 (0%)	1 (13%)	0 (0%)	1 (6%)
Fatigue	0 (0%)	1 (13%)	0 (0%)	1 (6%)

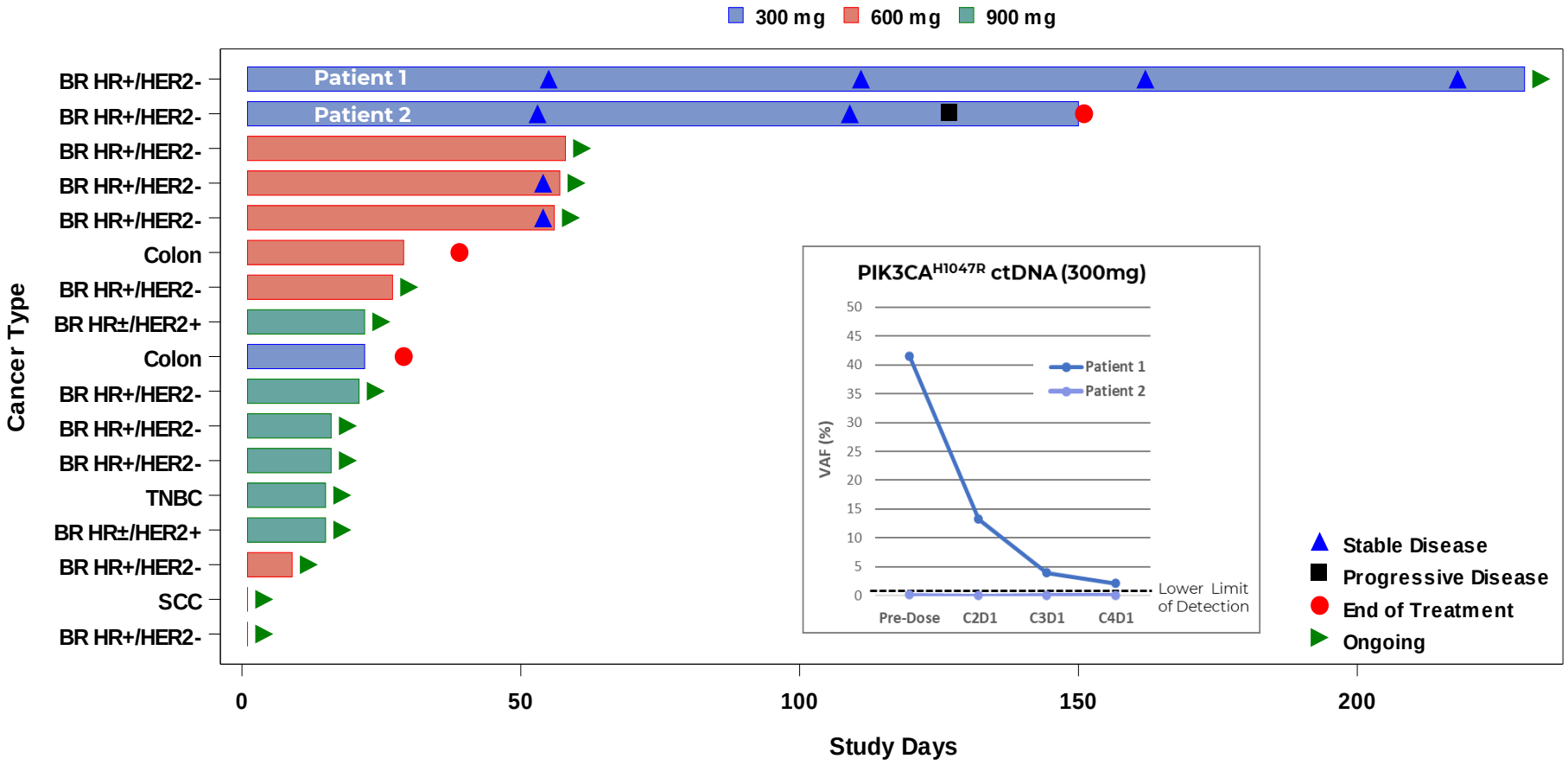
Data cut-off - October 28, 2024

- OKI-219 is well tolerated across all doses
- Adverse events were mild and infrequent
- No DLTs observed
- No dose interruptions, delays, reductions, or discontinuations for any AEs

TRAEs: Treatment Related Adverse Events; DLT: Dose Limiting Toxicities; AEs: Adverse Events

Time on Treatment

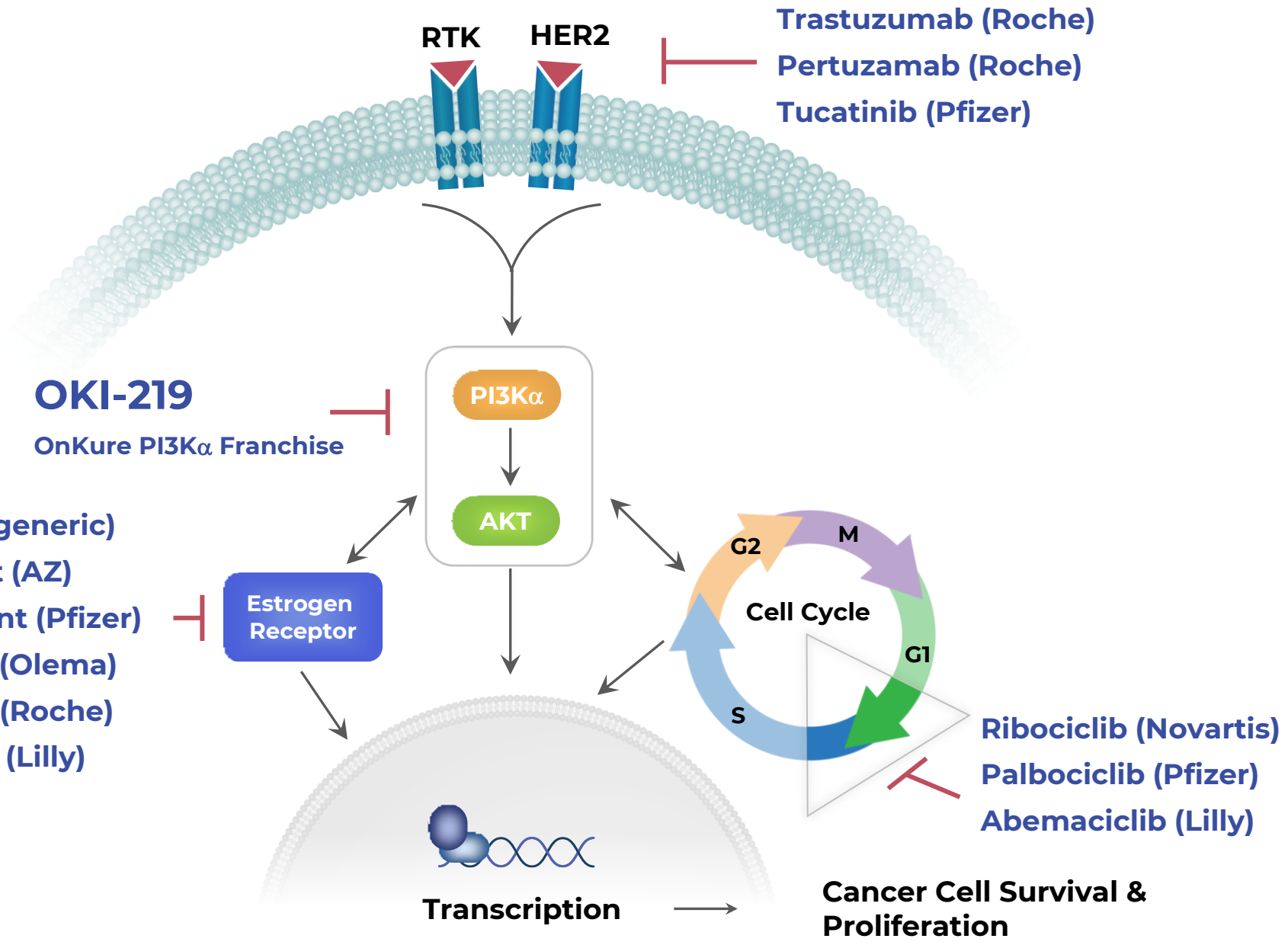
As of October 28, 2024



- 13/14 patients at doses ≥600 mg BID remain on study
- 2/3 patients at 300 mg showed prolonged stable disease
- Sustained >95% reduction in PIK3CA^{H1047R} ctDNA in 300 mg BID patient who remains on study after >7 months

OKI-219 Strategy:

Combine with Targeted Agents Across Breast Cancer



There are several next-generation agents in addition to the drugs noted here

Financial Overview

As of October 4, 2024

Stock Symbol	NASDAQ: OKUR
Investors Participants in Private Placement (Oct 2024)	Acorn Bioventures, Cormorant Asset Management, Surveyor Capital (a Citadel company), Perceptive Advisors, Deep Track Capital, Samsara BioCapital, Vestal Point Capital and other undisclosed investors
Cash and Investments	Approximately $139 million at close of the merger/private placement
Cash Runway	Cash and investments expected to provided funding through multiple clinical data readouts and runway into 4Q 2026
Common Stock Outstanding	Approximately 13.3 million shares outstanding October 4, 2024 (after the close of the merger/private placement, and post-reverse split)

acorn BIOVENTURES · PERCEPTIVE ADVISORS · CORMORANT ASSET MANAGEMENT · DEEP TRACK CAPITAL · SURVEYOR · SAMSARA BIOCAPITAL

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Summary: OnKure is Developing Innovative Precision Medicines for Patients

Mutation-specific approach to a **validated target (PI3Kα)** in a large patient population

Ongoing PIKture-01 trial evaluating OKI-219 single agent and in combination with other agents

Focused team with remarkable success in precision medicine

Supported by **committed investors**

OnKure® THERAPEUTICS

WRITING THE NEXT CHAPTER IN

PRECISION MEDICINES

FOR PATIENTS WITH CANCER