



2,938,005 Shares of Class A Common Stock

This prospectus supplement updates and amends the prospectus dated October 30, 2024 (as supplemented to date, the “Prospectus”), which forms a part of our Registration Statement on Form S-1 (Registration Statement No. 333-282792) originally filed with the Securities and Exchange Commission (the “SEC”) on October 23, 2024 and declared effective by the SEC on October 30, 2024, with the information contained in our Current Report on Form 8-K filed with the SEC on December 10, 2024, excluding the information that was furnished and not filed under Item 7.01 and the related Exhibits 99.1 and 99.2 furnished under such report (the “Current Report”).

This prospectus relates to the resale by certain of the selling securityholders named in this prospectus (each a “selling securityholder” and, collectively, the “selling securityholders”) of 2,938,005 shares of Class A Common Stock, par value \$0.0001 per share (the “Common Stock”) issued in the PIPE Financing (as defined in the Prospectus). The Prospectus also covers any additional securities that may become issuable by reason of stock splits, stock dividends or other similar transactions.

This prospectus supplement should be read in conjunction with the Prospectus, which is to be delivered with this prospectus supplement. This prospectus supplement updates, amends and supplements the information included or incorporated by reference in the Prospectus. If there is any inconsistency between the information in the Prospectus and this prospectus supplement, you should rely on the information in this prospectus supplement.

This prospectus supplement is not complete without, and may not be delivered or utilized except in connection with, the Prospectus, including any amendments or supplements to it.

Current Report on Form 8-K

On December 10, 2024, we filed the Current Report with the SEC. The Current Report is attached hereto.

We are an “emerging growth company,” as defined under the federal securities laws, and, as such, may elect to comply with certain reduced public company reporting requirements for future filings.

Investing in our securities involves a high degree of risk. Before buying any securities, you should carefully read the discussion of the risks of investing in our securities in the section titled “[Risk Factors](#)” beginning on page 7 of the Prospectus.

You should rely only on the information contained in the Prospectus, this prospectus supplement, or any further prospectus supplement or amendment hereto. We have not authorized anyone to provide you with different information.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus supplement is December 10, 2024.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 10, 2024

OnKure Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction
of Incorporation)

001-40315
(Commission File Number)

47-2309515
(IRS Employer
Identification No.)

6707 Winchester Circle, #400
Boulder, Colorado
(Address of Principal Executive Offices)

80301
(Zip Code)

Registrant's Telephone Number, Including Area Code: 720 307-2892

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Class A Common Stock, par value \$0.0001 per share	OKUR	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 7.01 Regulation FD Disclosure.

On December 10, 2024, Onkure Therapeutics, Inc. (the “Company”) issued a press release announcing preliminary safety, tolerability, and pharmacokinetic data from its first-in-human PIKture-01 trial of OKI-219. The press release is attached hereto as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

On December 10, 2024, the Company also posted a presentation to its Investor Relations website (<https://investors.onkuretherapeutics.com>). A copy of the presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Item 7.01, including Exhibits 99.1 and 99.2 attached hereto, shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

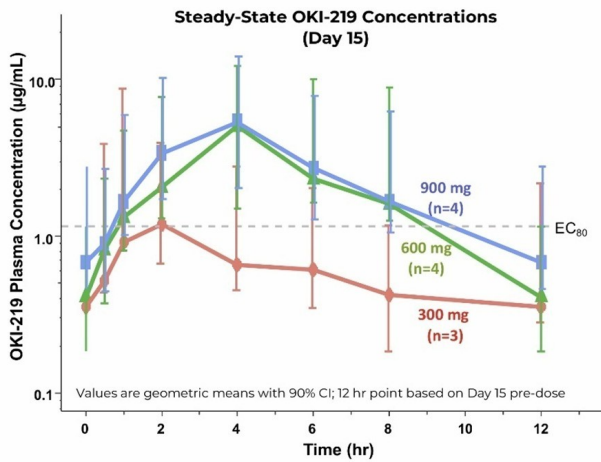
On December 10, 2024, the Company announced preliminary safety, tolerability, and pharmacokinetic (“PK”) data from its first-in-human PIKture-01 trial of OKI-219. OKI-219 was well tolerated across all dose levels with no hyperglycemia, and only grade 1 treatment-related adverse events (“TRAEs”) were reported. No dose interruptions, delays, reductions, or discontinuations were reported for any adverse events. OKI-219 dosed at 900 mg twice daily shows steady-state exposure levels with near-continuous coverage of the *in vivo* EC 80 for pAKT inhibition. These data support initiation of Part 1b of PIKture-01 evaluating OKI-219 in combination with fulvestrant, and the first patients have been dosed. The Company expects to provide additional single agent data and initial combination data with fulvestrant in the second half of 2025. In addition, the Company announced new pre-clinical data that show OKI-219’s synergistic activity, inducing regressions, in combination with SERD + CDK4/6 inhibitors.

Preliminary Safety Data (Data cutoff date for announcement: October 28, 2024)

Patients have been treated with OKI-219 at three dose levels as a single agent: 300 mg BID, 600 mg BID, and 900 mg BID. Across all three levels, a total of 17 patients have been dosed, including 11 patients with HER2- breast cancer, two with HR+/HER2+ breast cancer, two with colorectal cancer, one with triple negative breast cancer and one with squamous cell carcinoma in the single-agent dose escalation. OKI-219 has been generally well tolerated, with no dose-limiting toxicities, dose interruptions, or dose reductions required. The most common TRAEs were Grade 1 diarrhea (N=4), Grade 1 nausea (N=2) and Grade 1 pruritus (N=2).

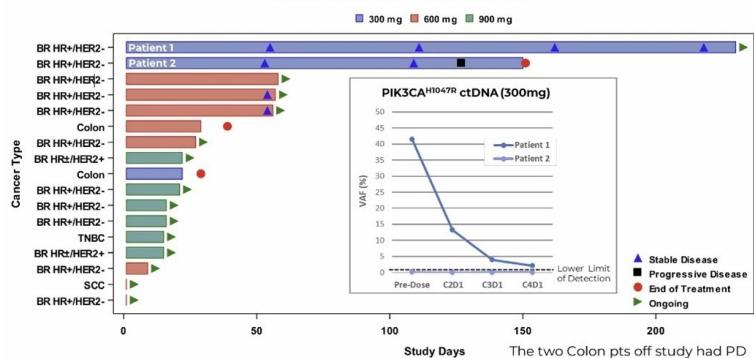
Pharmacokinetic and Selectivity Profile

OKI-219 has shown favorable PK data that support pharmacologically relevant exposures, even at the lowest assessed dose levels, with a safety profile that suggests little or no inhibition of wild-type PI3Kα. At steady state, the exposures of OKI-219 exceed exposures associated with robust antitumor activity in preclinical models.



There are 13 patients who have received a ≥ 600 mg dose twice a day that remain in the study. In addition, two patients with HR+/HER2- breast cancer (BR) who received the 300 mg dose showed prolonged stable disease, including one patient that sustained $>95\%$ reduction in PIK3CA^{H1047R} ctDNA and remains on treatment for more than seven months.

Time on Treatment



Pre-Clinical Data

Preclinical *in vivo* data show that OKI-219 used in combination with standard-of-care therapies for mutant-selected solid tumors, including breast cancers, showed potent anti-tumor activity with excellent tolerability at doses well above those needed for tumor regressions in those models. Specifically, OKI-219 shows strong combination activity in doublet with SERDs and in triplet with SERD + CDK4/6 inhibitors. Additional preclinical combination studies are ongoing.

Pipeline Progress

OnKure is actively pursuing multiple additional early-stage discovery programs that target oncogenic mutations of PI3K α . The Company has broadened the expectations of its next-generation program beyond PI3K α ^{H1047R} mutations to target all the most common PI3K α mutations (i.e., H1047R, E545K, and E542K). The Company expects to announce a pan-mutant development candidate in the first half of 2025. Additionally, the Company is developing a highly selective allosteric inhibitor molecule specifically targeting the PI3K α E545K and E542K mutations (a/k/a helical domain mutations or e-mutants) and expects to announce a development candidate in 2026.

Forward Looking Statements

The Company cautions you that statements contained in this report regarding matters that are not historical facts are forward-looking statements. These statements are based on the Company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding the potential of, and expectations and plans regarding, the Company's product candidates and programs, including OKI-219; the timing of data release for the ongoing clinical trial of OKI-219; and the Company's ability to advance additional programs, including the Company's discovery programs and the timing of announcement of development candidates for such programs. Actual results may differ from those set forth in this presentation due to the risks and uncertainties inherent in the Company's business, including, without limitation: the Company'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, the Company's product candidates; the outcome of preclinical testing and early clinical trials for the Company'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; the Company'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 the Company's current or future product candidates in combination with other therapies and the cost of combination therapies; the Company's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition the Company faces in discovering, developing, or commercializing products; the ability to attract, hire, and retain highly skilled executive officers and employees; the ability of the Company to protect its intellectual property and proprietary technologies; the scope of any patent protection the Company obtains or the loss of any of the Company's patent protection; developments relating to the Company'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 the Company files from time to time with the Securities and Exchange Commission (“SEC”), including the Quarterly Report on Form 10-Q for the period ended September 30, 2024, filed on November 7, 2024, the final 424B3 proxy statement/prospectus filed with the SEC on August 26, 2024, and any subsequent filings with the SEC. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and the Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release, dated December 10, 2024.
99.2	Presentation, dated December 10, 2024.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ONKURE THERAPEUTICS, INC.

Date: December 10, 2024

By: /s/ Jason Leverone
Name: Jason Leverone
Title: Chief Financial Officer

OnKure Announces Encouraging Preliminary Safety, Tolerability, and Pharmacokinetic (PK) Data from its First-In-Human PIKture-01 Trial of OKI-219

-- OKI-219 is well-tolerated across all doses, and no dose interruptions, delays, reductions, or discontinuations were reported

-- Initial patient data show exposures of OKI-219 exceeding levels associated with robust antitumor activity in preclinical models

-- Data support the initiation of Part 1b of PIKture-01 evaluating OKI-219 in combination with fulvestrant; first patients dosed, and initial data are expected in 2H-2025

-- Management to host conference call today, December 10, 2024 at 7:00 a.m. CT

BOULDER, CO, December 10, 2024 (GLOBE NEWSWIRE) – OnKure Therapeutics, Inc. (NASDAQ: OKUR), a clinical-stage biopharmaceutical company focused on the development of novel precision medicines in oncology, today announced encouraging safety, tolerability, and pharmacokinetic data from the ongoing first-in-human trial of OKI-219, a potential best-in-class, mutant-selective PI3K α^{H1047R} inhibitor. OKI-219 was well tolerated across all dose levels with no hyperglycemia, and only grade 1 treatment-related adverse events (TRAEs) were reported. No dose interruptions, delays, reductions, or discontinuations were reported for any adverse events (AEs). OKI-219 dosed at 900 mg twice daily shows steady-state exposure levels with near-continuous coverage of the *in vivo* EC 80 for pAKT inhibition. These data are consistent with the Company's preclinical data and support the continued development of OKI-219.

In addition, the Company announced new pre-clinical data that show OKI-219's synergistic activity, inducing regressions, in combination with SERD + CDK4/6 inhibitors, potentially paving the way for clinical trials in multiple lines of therapy. These clinical and preclinical data are scheduled to be presented during poster sessions at the 2024 San Antonio Breast Cancer Symposium (SABCS) on December 12, 2024.

"We are thrilled to present the first clinical data for our lead program, OKI-219, which is the only highly selective PI3K α^{H1047R} inhibitor molecule in the clinic," said Nicholas Saccomano, Ph.D., President and Chief Executive Officer of OnKure. "These preliminary data show that OKI-219 was very well tolerated and presents a favorable safety profile. In addition, the clinical PK data show consistent steady-state exposure with near-continuous target coverage at levels where clinical activity is consistently observed. These initial clinical data support our initiation of Part 1b of the PIKture-01 trial to evaluate OKI-219 in combination with fulvestrant. We look forward to providing mature single agent and initial fulvestrant data in the second half of 2025."

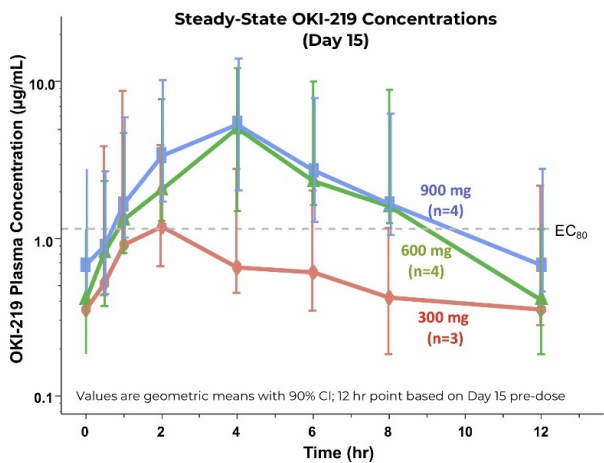
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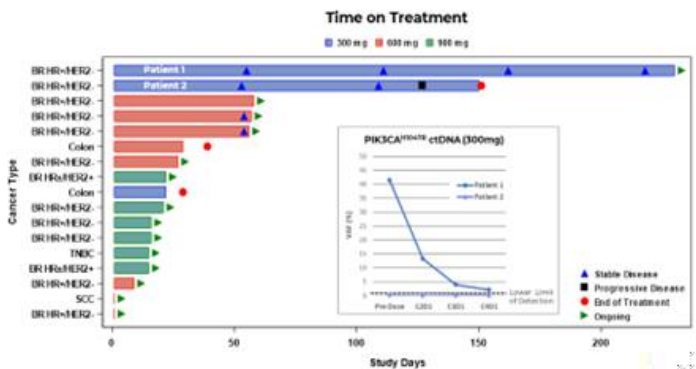
reductions required. The most common TRAEs were Grade 1 diarrhea (N=4), Grade 1 nausea (N=2) and Grade 1 pruritus (N=2).

Pharmacokinetic and Selectivity Profile

OKI-219 has shown favorable PK data that support pharmacologically relevant exposures, even at the lowest assessed dose levels, with a safety profile that suggests little or no inhibition of wild-type PI3K α . At steady state, the exposures of OKI-219 exceed exposures associated with robust antitumor activity in preclinical models.



There are 13 patients who have received a ≥ 600 mg dose twice a day that remain in the study. In addition, two patients with HR+/HER2- breast cancer (BR) who received the 300 mg dose showed prolonged stable disease, including one patient that sustained $>95\%$ reduction in PIK3CA^{H1047R} ctDNA and remains on treatment for more than seven months.





PIKture-01 Trial

PIKture-01 is a global, multi-center, first-in-human phase 1a/1b study evaluating OKI-219 as monotherapy and in combination with fulvestrant or trastuzumab in subjects with advanced solid tumors including breast cancer harboring a PI3K α^{H1047R} mutation. In Phase 1a, subjects receive escalating oral doses of OKI-219 starting at 300 mg BID continuously. Phase 1b is assessing OKI-219 in combination with fulvestrant in patients with HR+/HER2- breast cancer, or with trastuzumab in patients with HER2+ breast cancer. The study also includes a dose optimization phase to evaluate the optimal combination doses of OKI-219 with fulvestrant or trastuzumab. Additional information about PIKture-01 may be found at www.ClinicalTrials.gov, using Identifier: NCT06239467.

Poster presentation details: Title: *Preliminary results from PIKture-01, a First-in-Human Study of OKI-219, a mutant selective inhibitor of PI3K α^{H1047R} , in mutant selected solid tumors including breast cancer*; Presentation ID: P3-08-19; Abstract Number: SESS-3634; Date and Time: Thursday, December 12, 2024 at 12:30 PM to 2:00 PM CST; Presenter: Alexander Spira, MD, PhD, et al. The poster is available on the Publications page of the OnKure website ([click here](#)).

Pre-Clinical Data

Preclinical *in vivo* data show that OKI-219 used in combination with standard-of-care therapies for mutant-selected solid tumors, including breast cancers, showed potent anti-tumor activity with excellent tolerability at doses well above those needed for tumor regressions in those models. Specifically, OKI-219 shows strong combination activity in doublet with SERDs and in triplet with SERD + CDK4/6 inhibitors. Additional preclinical combination studies are ongoing. The Company believes OKI-219's selectivity could provide increased safety both as a single agent and in combination.

Poster presentation details: Title: *OKI-219 enhances activity of SOC therapies in double and triple combinations in pre-clinical PI3K α^{H1047R} mutant breast cancer models*; Presentation ID: P4-12-20; Abstract Number: SESS-2240; Date and Time: Thursday, December 12, 2024 at 05:30 PM to 7:00 PM CST; Presenter: Molly Taylor, PhD, et al. The poster is available on the Publications page of the OnKure website ([click here](#)).

Pipeline Progress

OnKure is actively pursuing multiple additional early-stage discovery programs that target oncogenic mutations of PI3K α . The Company has broadened the expectations of its next-generation program beyond PI3K α^{H1047} mutations to target all the most common PI3K α mutations (i.e., H1047R, E545K, and E542K). The Company expects to announce a pan-mutant development candidate in the first half of 2025.

Additionally, the Company is developing a highly selective allosteric inhibitor molecule specifically targeting the PI3K α E545K and E542K mutations (a/k/a helical domain mutations or e-mutants) and expects to announce a development candidate in 2026. Overall, the aim of the Company's discovery engine is to deliver highly selective drug candidates that preserve wild-type PI3K α while effectively targeting the majority of PI3K α -mutated cancers, in breast and other cancers.

Conference Call

OnKure will host a conference call and live webcast today, December 10, 2024 at 7:00 a.m. CT (8:00 a.m. ET) to discuss the preliminary data from the PIKture-01 trial of OKI-219, which will be presented at



SABCS. To participate, please dial 877-407-0789 (domestic), 201-689-8562 (international) and refer to conference ID 13750009. To access the webcast, click here. Following the live event, a replay will be also available on the Events page of the Investors section of the Company's website.

About OnKure

OnKure is a clinical-stage biopharmaceutical company focused on the discovery and development of best-in-class precision medicines that target biologically validated drivers of cancers that are underserved by available therapies. Using a structure-based drug design platform, OnKure is building a pipeline of tumor-agnostic candidates that are designed to achieve optimal efficacy and tolerability. OnKure is currently developing OKI-219, a selective PI3K α^{H1047R} inhibitor, as its lead program. OnKure aims to become a leader in targeting oncogenic PI3K α and has multiple programs designed to enable best-in-class targeting of this key oncogene.

For more information about OnKure, visit us at www.onkure.com and follow us on LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this press release, including statements regarding our 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 timing of data release for the ongoing clinical trial of OKI-219; OnKure's ability to advance additional programs, including OnKure's discovery programs and the timing of announcement of development candidates for such programs; and statements by the Company's President and Chief Executive Officer. 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.

The Company 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 Company'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, the Company's product candidates; the outcome of preclinical testing and early clinical trials for the Company'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; the Company'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 the Company's current or future product candidates in combination with other therapies and the cost of combination therapies; the Company's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition the Company faces in discovering, developing, or commercializing products; the ability to attract, hire, and retain highly skilled executive



officers and employees; the ability of the Company to protect its intellectual property and proprietary technologies; the scope of any patent protection the Company obtains or the loss of any of the Company's patent protection; developments relating to the Company'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 ("SEC"), including the Quarterly Report on Form 10-Q filed with the SEC on November 7, 2024, the final 424B3 proxy statement/prospectus filed with the SEC on August 26, 2024, and any subsequent filings with the SEC. 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 press release.

This press release contains hyperlinks to information that is not deemed to be incorporated by reference into this press release.

Contact:

Dan Ferry
LifeSci Advisors
daniel@lifesciadvisors.com



Exhibit 99.2

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 PI3K α ^{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

PI3K α 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 PI3K α inhibitors **designed to preserve wild-type PI3K α while effectively targeting the majority of PI3K α -mutated cancers**

- OKI-219 is a PI3K α ^{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: PI3K α ^{PAN} and PI3K α ^{E542K, E545K} programs
- Cash and investments expected to provide funding through multiple clinical milestones and runway into Q4 2026

Leadership Team with Proven Experience



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



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



Dylan Hartley, Ph.D.
Chief Scientific Officer



Duncan Walker, Ph.D.
Chief Development Officer



Jason Leverone
Chief Financial Officer



Rogan Nunn, J.D.
General Counsel and Secretary



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



Ann Howell, Pharm.D.
VP of Regulatory Affairs



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



Robbie Alton, Pharm
VP of Clinical Operations



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



Jim Wong, Ph.D.
VP of Biological Sciences



Mutant-Selective PI3K α Inhibitors

Targeting the Majority of PI3K α -mutated Cancers While Preserving Wild-type PI3K α

Program/Target	Indication(s)	Discovery	Preclinical	Clinical	Current Status	Next Anticipated Milestone
PI3K α mutant-specific portfolio	OKI-219 PI3K α ^{H1047R} mutant-selective inhibitor	PIKture-01 Trial			Phase 1 enrolling	Data Update (2H 2025)
	OKI-TBD PI3K α ^{PAN} mutant-selective inhibitor				Candidate selection	Select candidate (1H 2025)
	OKI-TBD PI3K α ^{E542K, E545K} mutant-selective inhibitor				Active discovery	Select candidate (2026)



PI3K α : The Most Commonly Mutated Oncogene

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

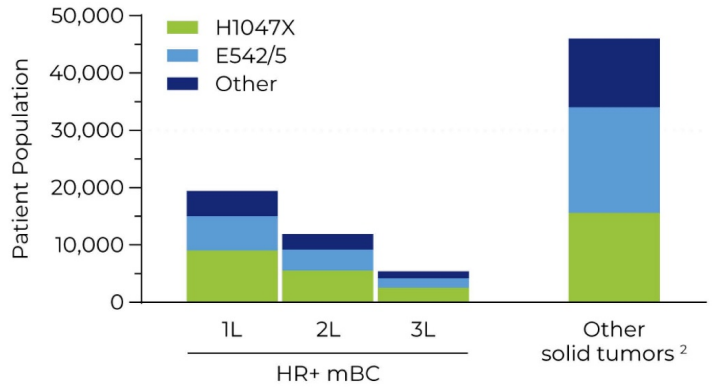
PI3K α : A validated target in HR+ MBC

- 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

- PI3K α ^{H1047R}* OKI-219, in Phase 1
- PI3K α ^{PAN} candidate selection 1H 2025
- PI3K α ^{E542K, E545K} active discovery

US Patient Population¹

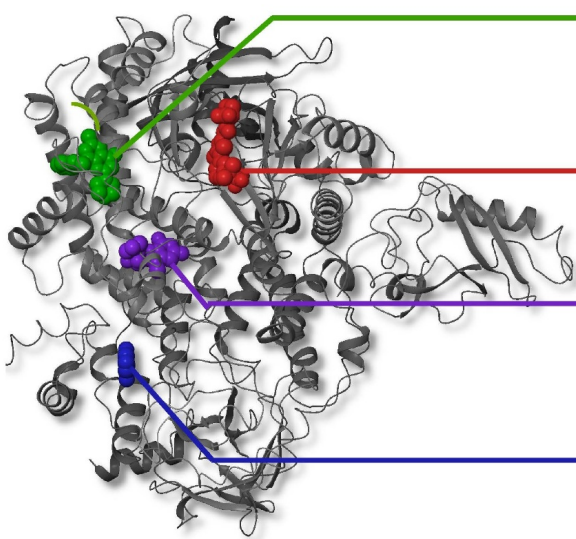


*PI3K α ^{H1047R} is the most common hot spot mutation³ present in ~15% of breast and ~4% of all human cancers⁴

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. T Kancovich, C, McLellan, M, Vardiri, F et al. Nature 502, 333-339 (2015); <http://www.tumorportal.org/igene>
4. <https://cancer.sanger.ac.uk/cosmic/gene/analysis?id=PIK3CA#references>
5. Fritsch et al Mol Cancer Ther; 13(5) May 2014, 6. Juric et al, JCO, 36 (13), 2018

Next-Gen PI3K α Mutant-Targeting Landscape

Mutant-Selectivity is Necessary to Drive Improved Efficacy and Safety



PI3K α ^{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

PI3K α ^{E-mutant} Inhibitors

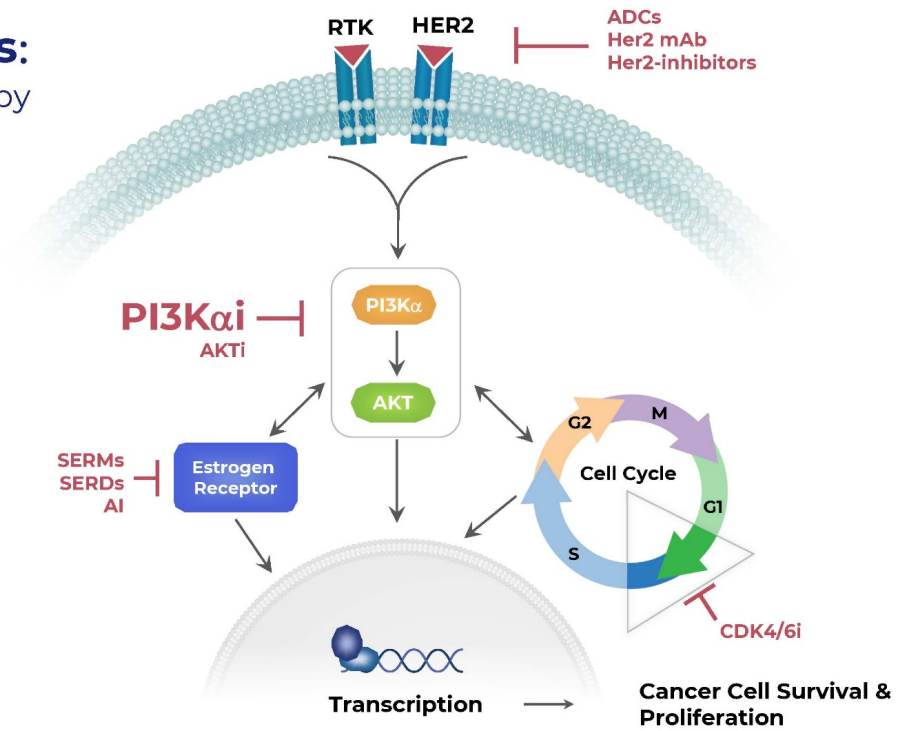
- E-mutation-specific
- No known clinical trials
- OnKure preclinical program

Reported Cell-Based Selectivity for PI3K α ^{H1047R} vs PI3K α ^{WT}

Compound	H1047R
Alpelisib ¹	1
STX-478 ¹	8.8
RLY-2608 ²	3.8
OKI-219³	~100

PI3K α ^{MUT} Inhibitors:

Potential Backbone Therapy
in Combination with
Approved Agents in
Breast Cancer



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



PI3K α Mutated HR+ MBC: A Major Market Opportunity

PI3K α ^{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
1 st Line	INAVOLISIB + palbociclib + fulvestrant	~9K
2 nd Line	ALPELISIB + fulvestrant CAPIVASERTIB + fulvestrant	~5.5K

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**

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

OKI-219: Multiple Development Opportunities

The Potential to Reach Across Multiple Lines of Therapy

PI3K α ^{H1047R} Mutant-Selective Drugs: Development into Poorly Served Markets

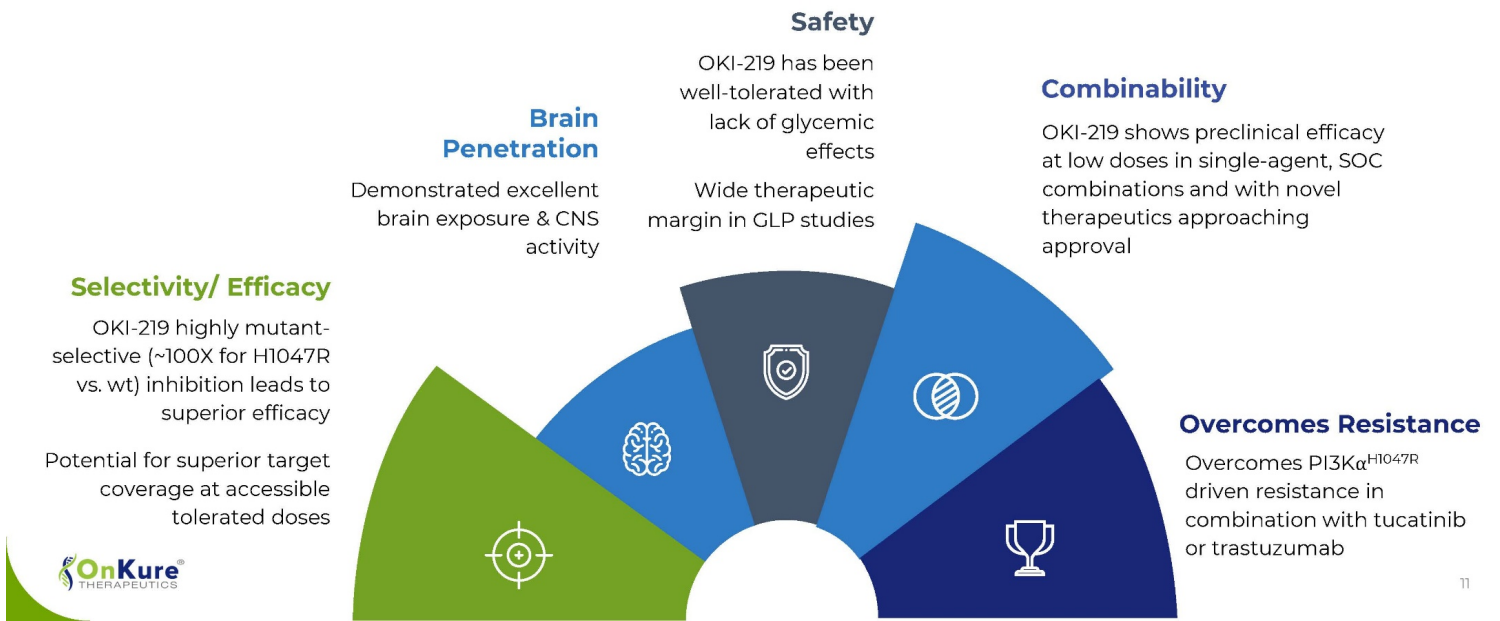
	Current & Near-Term Treatments	OKI-219 Development Opportunities (Start in Metastatic and Advance to Adjuvant)	
Adjuvant	NONE (AI +/- CDK4/6)	OKI-219 vs. Placebo (SOC) (AI+CDK4/6 Combo)	
1st Line	INAVOLISIB + palbociclib + fulvestrant	OKI-219 vs. Placebo (SOC) <i>>12 months prior AI+ CDK4i</i> (AI+CDK4/6 Combo)	OKI-219 vs. Inavolisib <i><12 months prior AI+ CDK4i</i> (AI+CDK4/6 Combo)
2nd Line	ALPELISIB + fulvestrant	OKI-219 vs. Placebo (SOC) <i>prior inavolisib or alpelisib</i> OKI-219 + SERD	OKI-219 vs. alpelisib/capivasertib OKI-219 + next gen SERD
	CAPIVASERTIB + fulvestrant		

OKI-219 Approval Strategy



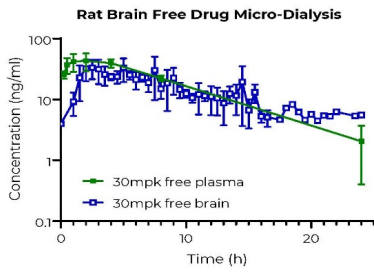
SOC: Standard of Care

Preclinical Safety and Efficacy Profile Shows High Potential

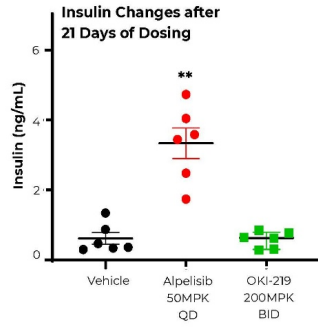


Preclinical Safety and Efficacy Profile Shows High Potential

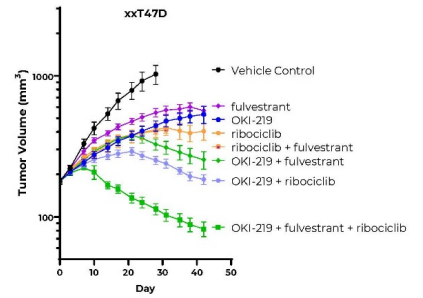
Brain Penetration



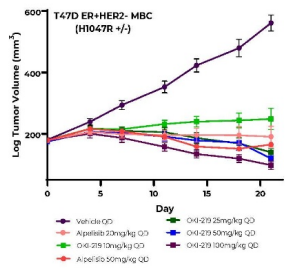
Safety



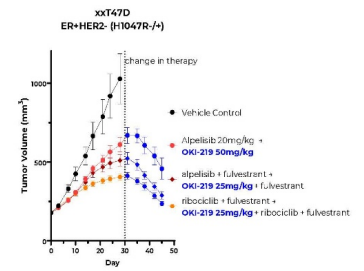
Combinability



Selectivity/ Efficacy

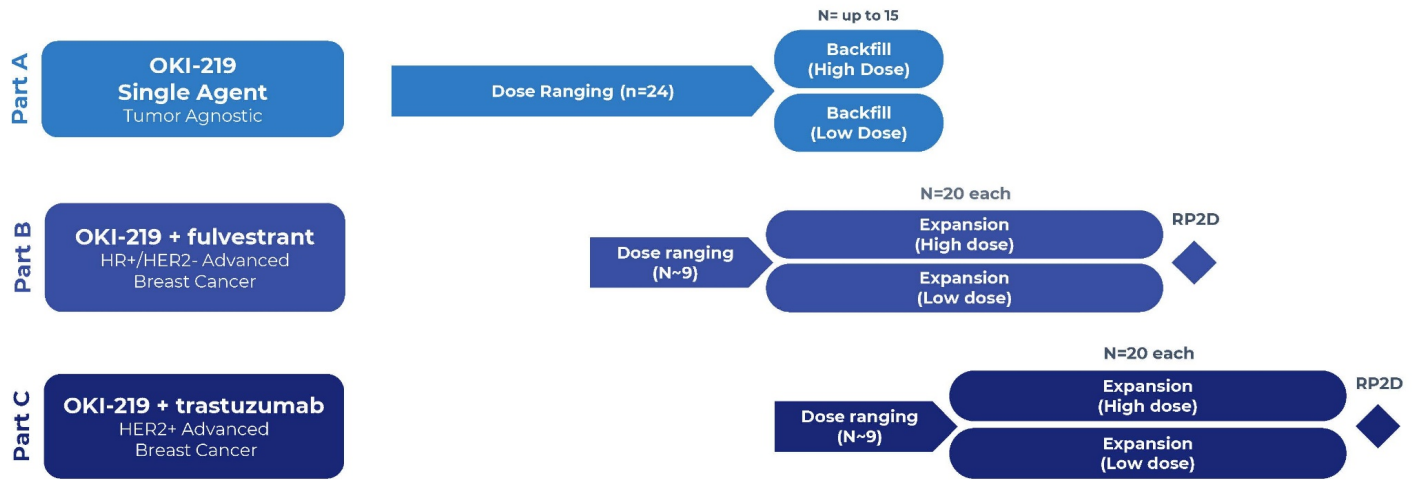


Overcomes Resistance



PIKture-01 Phase 1 Clinical Trial

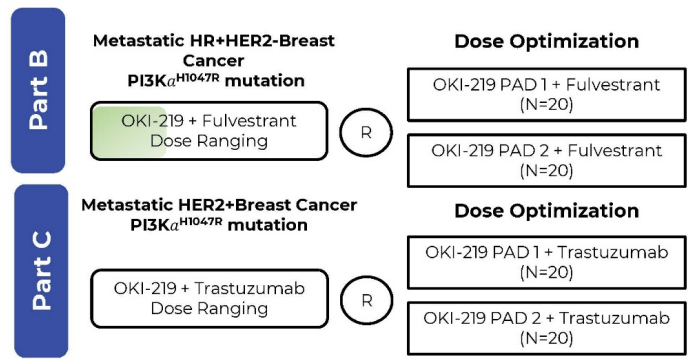
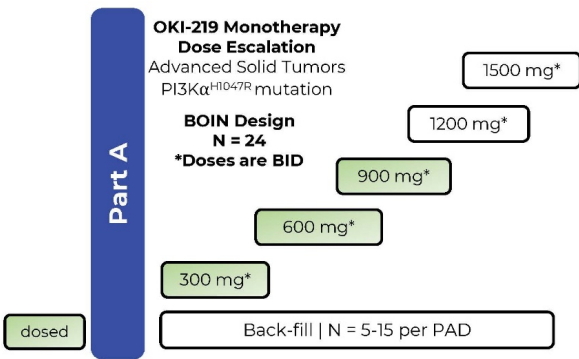
An Open-Label, Multicenter, Dose-Escalation First-in-Human Trial of OKI-219



Additional expansion combination arms are being planned

PIKture-01 Study Design

As of October 28, 2024



Key Eligibility Criteria:

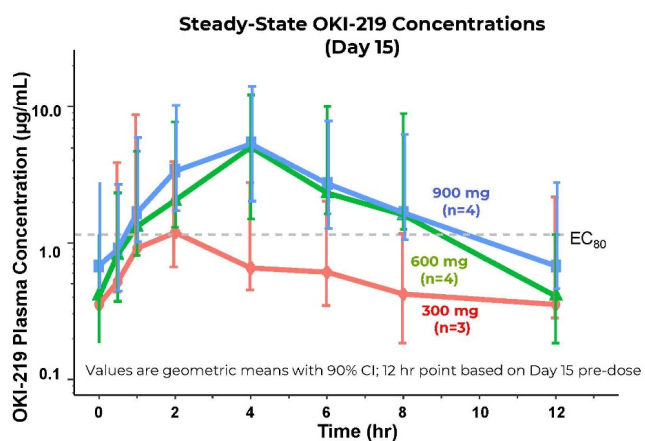
- PI3K α^{H1047R} advanced solid tumors who received prior SOC
- Prior PIK3 inhibitors of any kind allowed
- Treated or untreated asymptomatic brain metastasis allowed
- HbA1C < 8% allowed

Key Endpoints:

- Safety and tolerability
- PK, PD, RP2D incorporating Project Optimus¹
- 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

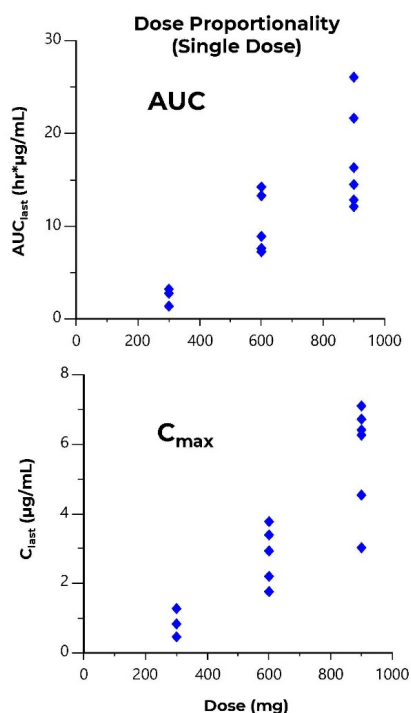
Pharmacokinetics: Highly Developable Candidate Profile



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%)

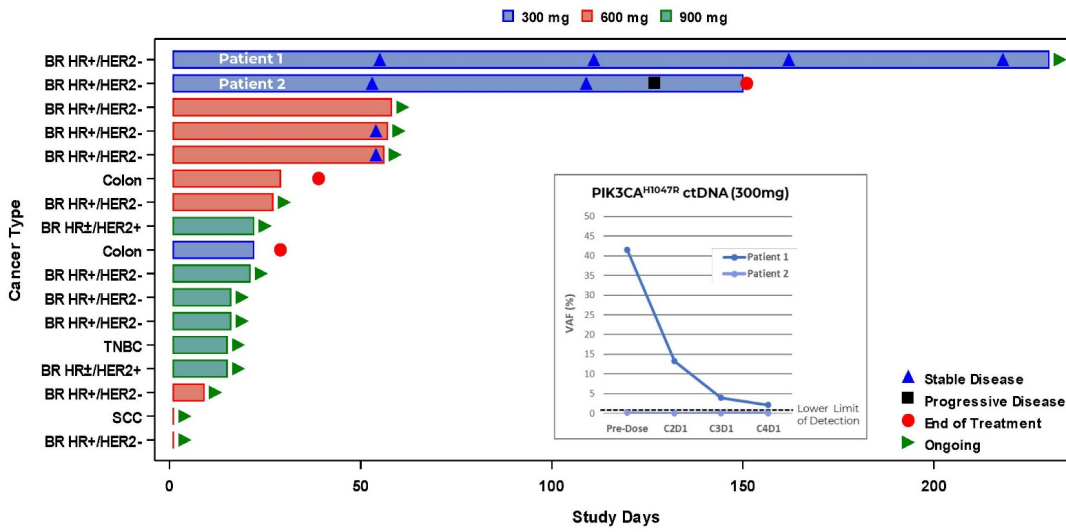
Data cut-off - October 28, 2024

- 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

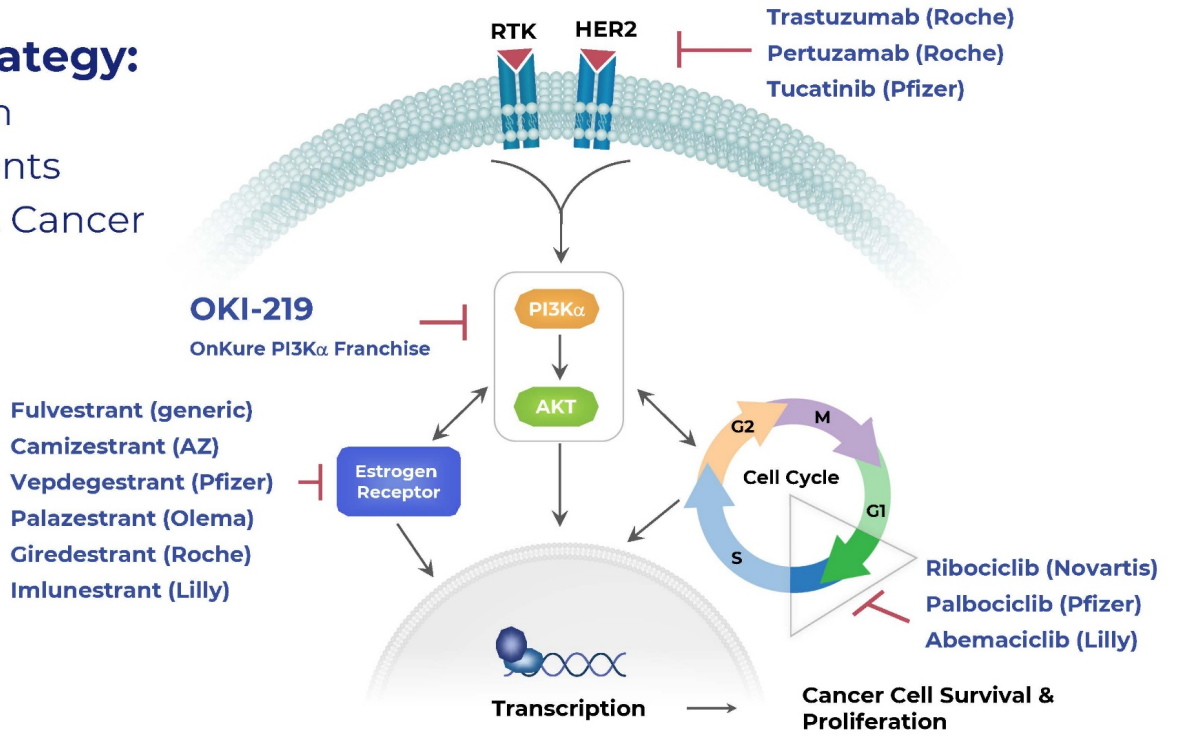
As of October 28, 2024



- 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



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)



Summary: OnKure is Developing Innovative Precision Medicines for Patients

Mutation-specific approach to a **validated target (PI3K α)** 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**





WRITING THE NEXT CHAPTER IN
PRECISION MEDICINES
FOR PATIENTS WITH CANCER

