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

December 10, 2024

-- 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

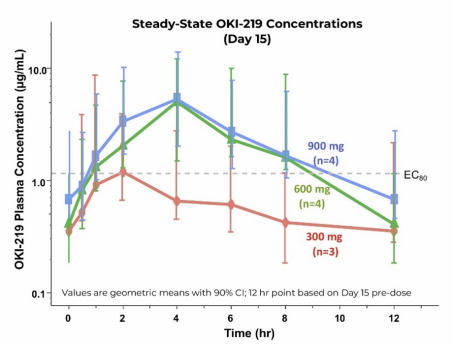
-- Data support the initiation of Part 1b of PIKture-01 evaluating OKI-219 in combination with fulvestrant; first patients dosed, and initial data are expected in 2H-2025

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

BOULDER, Colo., Dec. 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 PI3Kα^{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.

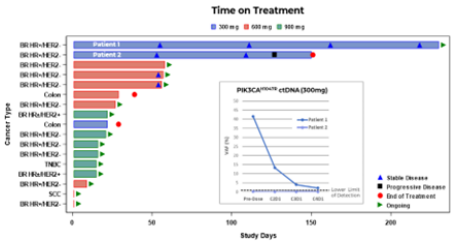
In addition, the Company announced new pre-clinical data that show OKI-219's synergistic activity, inducing regressions, in combination with SERD + CDK4/6 inhibitors, potentially paving the way for clinical trials in multiple lines of therapy. These clinical and preclinical data are scheduled to be presented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

Figure 1



Steady-State OKI-219 Concentrations (Day 15)

Figure 2



Time on Treatment

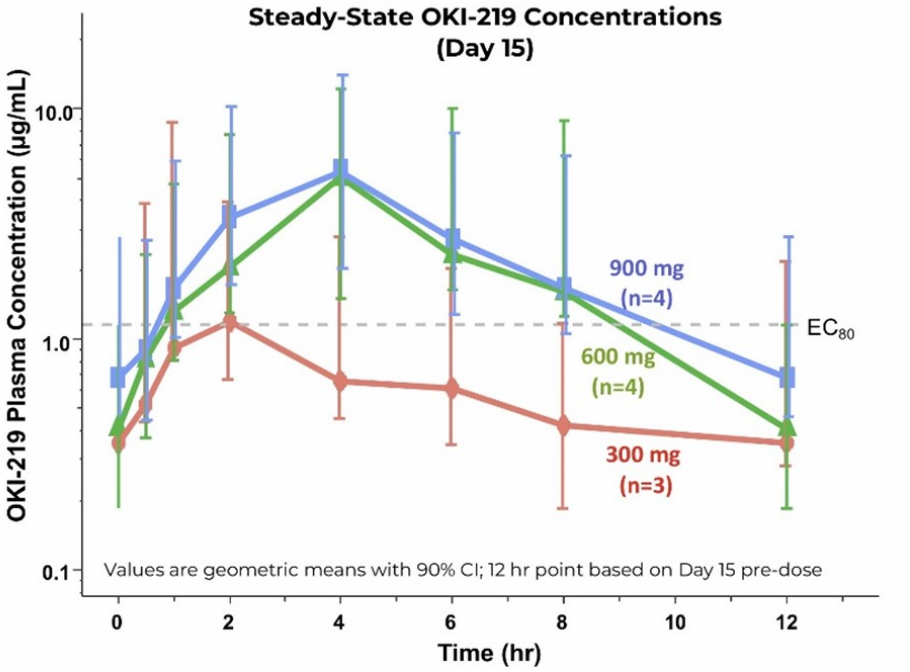
"We are thrilled to present the first clinical data for our lead program, OKI-219, which is the only highly selective PI3Kα^{H1047R} inhibitor molecule in the clinic," said Nicholas Saccomano, Ph.D., President and Chief Executive Officer of OnKure." These preliminary data show that OKI-219 was very well 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."

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

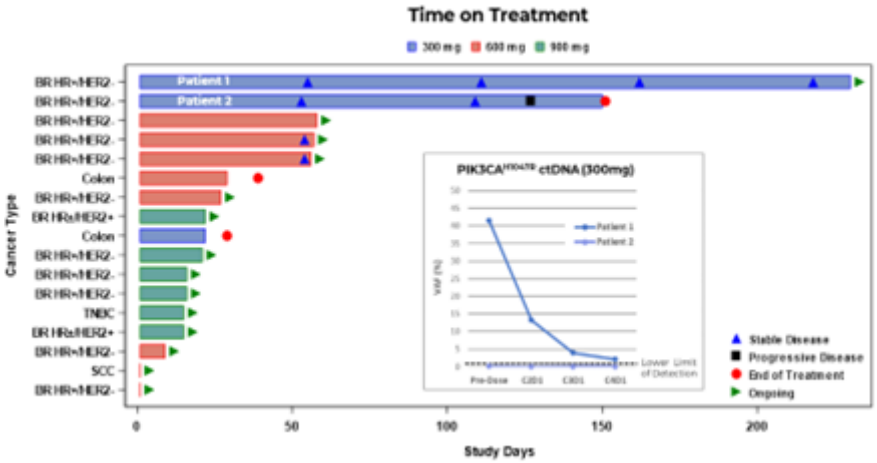
Patients have been treated with OKI-219 at three dose levels as a single agent: 300 mg BID, 600 mg BID, and 900 mg BID. Across all three levels, a total of 17 patients have been dosed, including 11 patients with HR+/HER2- breast cancer, two with HER2+ breast cancer, two with colorectal cancer, one with 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.



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 PI3Kα^{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 PI3Kα^{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 PI3Kα^{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 PI3Kα. The Company has broadened the expectations of its next-generation program beyond PI3Kα^{H1047} mutations to target all the most common PI3Kα 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 PI3Kα 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 PI3Kα while effectively targeting the majority of PI3Kα-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 PI3Kα^{H1047R} inhibitor, as its lead program. OnKure aims to become a leader in targeting oncogenic PI3Kα 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.

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Photos accompanying this announcement are available at

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