OnKure Announces IND Clearance by U.S. FDA Enabling Phase 1 Initiation for its Mutant Selective PI3Kα inhibitor, OKI-219

January 4, 2024

BOULDER, Colorado – January 4, 2024 – OnKure, Inc. today announced that the U.S. Food and Drug Administration (FDA) has cleared the Investigational New Drug (IND) application of OKI-219, a potential best-in-class, mutant selective PI3Kα^{H1047R} inhibitor, for clinical evaluation. H1047R is the most common mutation in PI3Kα, being found in 15% of breast cancer and 4% of cancers overall.

There is a significant need for improved therapies targeting PI3Kα with safer and more effective drugs. OKI-219 is a highly selective inhibitor of PI3Kα^{H1047R}, with over 100-fold selectivity for the wild-type enzyme, potentially sparing on-target toxicities that arise from inhibition of the wild-type form of the protein in normal tissues. OKI-219 shows strong, single-agent activity, including regressions at low doses in multiple PI3Kα^{H1047R} xenograft models that are heterozygous for PI3Kα^{H1047R}, the most common profile seen clinically for this mutation, and supporting the potential activity of highly mutant-selective inhibitors. Notably, in preclinical models, OKI-219 shows no evidence of toxicities related to PI3Kα wild-type inhibition as measured by markers of hyperglycemia, even at doses that are >15x higher than minimally active doses for antitumor activity.

Mutational activation of PI3Kα is associated with lower activity of both estrogen receptor (ER)-targeted and HER2-targeted agents in breast cancer. OKI-219 shows synergistic activity in combination with selective estrogen receptor degraders (SERDs), overcoming SERD resistance and driving strong regressions. Similarly, the combination of OKI-219 + tucatinib drives strong regressions in models of HER2+/ PI3Kα^{H1047R} breast cancer that are resistant to HER2- inhibitors.

OnKure plans to initiate a first-in-human clinical trial, OKI-219-101 (PIKture-01), in the first quarter of 2024 that will include a dose escalation in patients with advanced solid tumors harboring the PI3Kα^{H1047R} mutation. Subsequent evaluation of OKI-219 in combination with the SERD fulvestrant in ER+/ PI3Kα^{H1047R} advanced breast cancer, and with the HER2-monoclonal antibody trastuzumab in HER2+/ PI3Kα^{H1047R} advanced breast cancers will follow.

About PI3Kα and OKI-219

PI3Kα is the most frequently mutated oncogene in cancers, and PI3Kα^{H1047R} is the most common mutation in this gene, being found in 15% of breast cancer and 4% of cancers overall. While novel drugs targeting PI3Kα have been approved, the lack of mutant selectivity of these therapeutics drives considerable on-target toxicity by inhibiting the normal version of this protein in various tissues. To address this challenge, OnKure is discovering and developing a platform of highly mutant-selective PI3Kα inhibitors with the goal of improving efficacy and safety with molecules that fully inhibit the mutant oncogene while sparing the wild-type enzyme in normal tissues. OKI-219 is a potential best-in-class, orally bioavailable, highly selective inhibitor of PI3Kα^{H1047R} with over 100-fold selectivity for the mutated form of the enzyme compared to wild-type. OnKure believes that the wild-type sparing properties of OKI-219 should significantly improve the activity and safety relative to currently approved agents. OKI-219 is currently in Phase 1 of clinical development in solid tumor patients with PI3Kα^{H1047R} mutations.

About OnKure

OnKure, Inc. 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 proven structure-based drug design platform, the Company is building a robust 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 the leader in targeting oncogenic PI3Kα and has multiple programs 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 X (formerly known as Twitter) and LinkedIn.