OnKure Therapeutics Announces Promising Preclinical Data on OKI-179 in RAS-Mutated Tumor Models Presented in a Late-Breaking Session at AACR

April 8, 2022

OKI-179 demonstrated chemical synthetic lethality when combined with MEK and BRAF inhibitors in RAS pathway mutated cancer models

The Company plans to initiate the OKI-179-230 Phase 1b/2 trial of OKI-179 in combination with Pfizer's MEK inhibitor, binimetinib, in advanced NRAS-mutated melanoma (the Nautilus trial) in the coming weeks

BOULDER, Colorado—April 8, 2022 — OnKure, Inc., a clinical-stage biopharmaceutical company discovering and developing the next generation of oncology precision medicines, today announced preclinical data demonstrating synergy between OKI-179, the Company's oral Class I histone deacetylase (HDAC) inhibitor, and RAS pathway agents, including Pfizer's MEK inhibitor, binimetinib, in RAS-mutated tumor models. The data will be disclosed in a late-breaking abstract during the American Association of Cancer Research (AACR) Annual Meeting, being held in New Orleans, Louisiana from April 8, 2022 to April 13, 2022.

"The preclinical data highlighting our HDAC inhibitor's synergy with RAS pathway agents are extremely promising, and based on the anti-tumor activity seen, strongly support the clinical development of this combination across multiple indications, including in cancer types less sensitive to RAS pathway inhibition alone," said Tony Piscopio, Ph.D., Co-Founder, President and Chief Executive Officer of OnKure. "OKI-179 has been designed to overcome the historic tolerability limitations of other HDAC inhibitors, supporting further development in rational combinations with other anti-cancer treatments. Since inhibition of the RAS pathway alone through MEK or BRAF inhibitors is often insufficient to drive tumor regression, it opens an opportunity for combination approaches with OKI-179, with the potential to establish this candidate as a backbone therapy for all RAS-mutated cancers."

The data, both *in vitro* and *in vivo*, showcase the potential of the synthetically lethal combination of OKI-179 and RAS pathway agents in treating RAS-mutated tumors. In cell-line derived xenograft models, OKI-179, binimetinib as a single agent, and binimetinib + encorafenib combination demonstrated tumor growth delay, but few regressions. OKI-179 combined with binimetinib in *NRAS*-mutated melanoma or combined with binimetinib + encorafenib in BRAF-mutated colorectal xenografts showed significantly increased regressions compared to either single agent following two weeks of dosing.

Jennifer Diamond, M.D., OnKure's Chief Medical Officer said, "We plan to initiate the Nautilus trial, which will explore the combination of OKI-179 and binimetinib in advanced *NRAS*-mutated melanoma, and look forward to continuing to validate this synthetically lethal combination across cancer types in order to fully understand its potential as a therapeutic approach."

The poster presentation from the AACR Annual Meeting is available on the "Publications" page of the Company's website at https://onkuretherapeutics.com/news-publications/publications/.

About *NRAS*-Mutated Melanoma

Activating mutations in *NRAS* is the second most common oncogenic driver in melanoma, accounting for 20% of all melanomas. Tumors bearing *NRAS* mutations are more aggressive and are associated with poorer patient outcomes. Despite the prevalence of *NRAS* mutations and the severity of the resulting disease, treatment options for *NRAS*-mutated melanoma remain limited for patients who have disease progression following immune checkpoint inhibitor therapy, highlighting the significant unmet need.

About OKI-179

OKI-179 is a novel, oral Class I histone deacetylase (HDAC) inhibitor for the potential treatment of a wide range of solid and hematological malignancies. HDAC inhibitors have shown little activity in treating solid tumors, often due to poor tolerability, inappropriate dosing regimens, and a lack of stratifying biomarkers. OKI-179 is designed to have improved potency, selectivity, tolerability, as well as easy combinability to overcome the historic limitations of other HDAC inhibitors. This candidate has also shown a promising safety profile in advanced solid tumor patients, supporting potential combination studies in the future.

About OnKure Therapeutics

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 cancer. Using its proven structure-based drug design approach, the Company is building a robust pipeline of tumor-agnostic candidates that are designed to achieve optimal tolerability and efficacy. OnKure is currently developing its lead clinical candidate, OKI-179, an oral, selective Class I HDAC inhibitor, for the treatment of both hematological and solid tumors.

For more information, please visit www.onkuretherapeutics.com and follow us on LinkedIn and Twitter.