

A promising new chapter for PI3K δ inhibition: Nature Communications publications reveal novel mechanism behind iOnctura's roginolisib

- [First publication](#) reveals how roginolisib uniquely locks the cancer-driving enzyme PI3K δ in an inactive state, differentiating the drug from other PI3K δ inhibitors
- [Second publication](#) outlines first-in-human (FiH) study results, demonstrating roginolisib's favorable tolerability profile and encouraging clinical findings in patients with cancer, including metastatic uveal melanoma (mUM)
- Publication of the peer-reviewed papers comes as iOnctura awaits readouts from its two fully-enrolled, randomized Phase II trials of roginolisib in mUM and non-small cell lung cancer (NSCLC)

Geneva, Switzerland; Amsterdam, The Netherlands; and Cambridge, Massachusetts, USA, October 9, 2026 – iOnctura, a clinical-stage precision oncology company combating neglected and hard-to-treat cancers, today announced the publication of two peer-reviewed articles in *Nature Communications* revealing new insights into the novel mechanism and clinical profile of roginolisib, the company's next-generation, conformation-selective PI3K δ inhibitor.

Catherine Pickering, CEO and co-founder of iOnctura, said: "These papers address a longstanding challenge in PI3K δ drug development: how to achieve potent inhibition of the target while maintaining selectivity. By revealing a new way of locking PI3K δ into an inactive state and pairing that discovery with compelling clinical findings, these studies open an exciting new chapter for selective pathway inhibition. The findings reinforce the potential of roginolisib as a differentiated therapeutic option across multiple cancers with significant unmet need."

Roginolisib's novel mechanism: locking PI3K δ in an inactive state

PI3K δ has long been recognized as an important therapeutic target in cancer, but previous generations of inhibitors have been severely limited by tolerability issues, associated in part with the way they bind to the enzyme. In this mechanistic study, researchers from the University of Geneva and the Max Planck Institute of Biophysics in Frankfurt used X-ray crystallography, molecular dynamics simulations and hydrogen-deuterium exchange mass spectrometry to investigate how roginolisib interacts with PI3K δ . They revealed a novel binding mode: roginolisib locks the enzyme into an inactive conformation by uniquely stabilizing its catalytic C-terminal helix α 12.

By inhibiting PI3K δ , roginolisib cuts production of PIP3, a key cellular signaling molecule that drives cancer.

Researchers from the University of Toulouse then discovered that, compared with PI3K δ inhibitor idelalisib, roginolisib was associated with more sustained suppression of PIP3 formation in tumor samples from patients with chronic lymphocytic leukemia (CLL). Notably, roginolisib also reduced PIP3 levels in samples from heavily pre-treated, double-refractory patients who were resistant to both ibrutinib and venetoclax, whereas idelalisib did not.

Gerhard Hummer, Director of Theoretical Biophysics at the Max Planck Institute of Biophysics and Professor of Biophysics at Goethe University Frankfurt said, “These findings are exciting because they uncover a novel mechanism for PI3K δ inhibition. By stabilizing the inactive conformation of PI3K δ , roginolisib inhibits the kinase in a fundamentally different way than conventional approaches. Our research also suggests the novel binding mode may have meaningful biological consequences beyond the structural level.”

FiH study highlights roginolisib’s favorable tolerability profile and clinical activity, supporting clinical relevance of novel PI3K δ inhibition mechanism

Key findings of the FiH study, which evaluated continuous daily dosing of roginolisib in 44 patients with advanced solid and hematological malignancies include:

- No dose-limiting toxicities and no dose modifications. Grade ≥ 3 toxicities considered related to roginolisib were reported in only 3 of 44 patients (6.8%).
- Treatment-associated reductions in regulatory T cells and increases in activated CD8+ T cells and circulating IL-15 were observed, supporting a rebalancing of the immune system towards an antitumor response.
- Median overall survival (OS) of 20.8 months in patients with metastatic uveal melanoma (mUM). A median OS of 7 months was observed in historical controls in patients receiving immunotherapies as second line treatment.¹ This difference in median OS triggered the ongoing randomized Phase II study OCULE-01.

The study incorporated an extensive translational research program (partly conducted in collaboration with the Karolinska Institute in Sweden and Radiomics.bio in Liege, Belgium), including radiomic imaging analyses, tumor and cell-free DNA profiling, circulating immune-cell analysis, plasma proteomics, tumor transcriptomics and immunohistochemistry.

Anna Maria Di Giacomo, Professor of Medical Oncology at the University of Siena, Italy, and Head of the Phase I Program at the University Hospital of Siena, Italy, first author of the paper, mentioned: “In this patient population a safe agent like roginolisib is not common and the length of treatment was remarkable from the very beginning.”

Michele Maio, Professor of Medical Oncology at the University of Siena, Italy, Director of the Center for Immuno-Oncology, of the Division of Medical Oncology and Immunotherapy, and of the Department of

¹ Rantala et al., Melanoma Res., 2019 Dec 29(6):561-568

Medical Oncology at the University Hospital of Siena, Italy, and co-principal investigator on the FiH study,

added: “The clear translation of roginolisib’s differentiated biology into the clinic is encouraging. Roginolisib demonstrated favorable tolerability with continuous daily dosing and showed encouraging signs of clinical activity, supporting the potential of this novel approach to PI3K δ inhibition for patients with uveal melanoma and other difficult-to-treat cancers.”

iOnctura is currently running a comprehensive Phase II program investigating roginolisib alone or in combination with standard of care treatments, such as immune checkpoint, kinase, BCL-2 inhibitors and chemotherapy:

- Phase II OCULE-01 study in patients with mUM ([NCT06717126](#))
- Phase II in patients with NSCLC in combination with chemotherapy and the PD-1 inhibitor dostarlimab ([NCT06879717](#))
- Phase I/II in patients with myelofibrosis who no longer respond to JAK inhibitors, in combination with a JAK inhibitor ([NCT06887803](#))

In addition, investigator-sponsored studies are ongoing in CLL patients who no longer respond to BTK inhibitors ([NCT06644183](#)); in peripheral T-cell lymphoma (PTCL) patients who have progressed on prior treatments ([NCT07018752](#)); and in mUM in combination with tebentafusp ([NCT07203391](#)).

To view the papers, please click the links below:

PI3K δ is selectively inhibited by roginolisib by stabilizing the C-terminal helix α 12

<https://www.nature.com/articles/s41467-026-77424-0>

DOI: 10.1038/s41467-026-77424-0

The conformation-selective PI3K δ inhibitor roginolisib in patients with advanced or metastatic cancer, including metastatic uveal melanoma: first-in-human clinical trial

<https://www.nature.com/articles/s41467-026-77358-7>

DOI: 10.1038/s41467-026-77358-7

ENDS

For more information contact:

Corporate Press Office:

press@iOnctura.com

Optimum Strategic Communications

Mary Clark / Stephen Adams / Henry Williams

Tel: +44 203 821 6420

ionctura@optimumcomms.com

About iOnctura

iOnctura is a clinical-stage precision oncology company combating neglected and hard-to-treat cancers with a pipeline of first-in-class small molecules. The bold new treatments extend lives and improve healthspans, changing the outlook for patients and their families. Lead asset, roginolisib, is the first conformation-selective inhibitor targeting the inactive form of PI3K δ . This novel binding mode allows for precise inhibition of PI3K δ , delivering clinical activity without the detrimental tolerability seen with previous generations of inhibitors. Roginolisib is being investigated in multiple randomized Phase II studies in solid and hematological malignancies. iOnctura is headquartered in Amsterdam, The Netherlands with subsidiaries located in Geneva, Switzerland and Cambridge, MA, USA. iOnctura is backed by specialist institutional investors including Syncona, M Ventures, Inkef Capital, EIC Fund, VI Partners, Schroders Capital and XGEN Venture.

About roginolisib

Roginolisib is a non-ATP-competitive PI3K δ inhibitor that stabilizes the catalytic C-terminal helix α 12, inducing an allosteric conformational shift that locks PI3K δ in its inactive state and prevents ATP-mediated activation. This novel binding mode allows for precise inhibition of PI3K δ , delivering clinical activity without the detrimental tolerability seen with previous generations of inhibitors. The PI3K signaling pathway is one of the most commonly dysregulated pathways across multiple cancer types. The potential of roginolisib has been validated by positive clinical signals in Phase I in solid tumor and hematological malignancies, including a doubling of overall survival compared to historical controls in rare eye cancer, uveal melanoma. The company has carefully designed its clinical portfolio to allow full development in uveal melanoma, while in parallel validating the program in larger market indications.

The randomized Phase II OCULE-01 study in uveal melanoma ([NCT06717126](#)) completed patient recruitment in December 2025, the PULMO-01 study in non-small cell lung cancer (NSCLC) ([NCT06879717](#)) completed recruitment in January 2026 and the HEMA-MED Phase I/II study ([NCT06887803](#)) in myelofibrosis began in November 2025 and recruitment is ongoing.