iOnctura initiates Phase I/II trial in patients with myelofibrosis ahead of new non-clinical data at ASH

- First patient dosed in Phase I/II HEMA-MED clinical trial (NCT06887803) evaluating the tolerability and efficacy profile of roginolisib (PI3Kδ inhibitor) plus ruxolitinib in myelofibrosis (MF) patients unresponsive to Janus kinase (JAK) inhibitors
- Dual-target approach: combining PI3Kδ and JAK inhibition addresses complementary disease mechanisms and may overcome unresponsiveness to JAK inhibitors in MF
- New supporting non-clinical data to be presented at the 67th American Society of Hematology (ASH) Annual Meeting in Orlando, Florida: Data from *ex-vivo* models of MF demonstrate roginolisib monotherapy activity and synergy with JAK inhibition

Geneva, Switzerland and Amsterdam, The Netherlands and Cambridge, Massachusetts, USA, December 4, 2025 - iOnctura, a clinical-stage biopharmaceutical company combating neglected and hard-to-treat cancers, today announces it has dosed the first patient in its Phase I/II clinical trial evaluating roginolisib in patients with MF who are no longer responding to JAK inhibition. Further details of the trial will be presented in a poster presentation at the 67th American Society of Hematology (ASH) Annual Meeting in Orlando, Florida on Sunday, December 7 at 6pm EST.

This milestone marks an important step toward addressing the significant unmet medical needs of MF patients who face diminishing therapeutic options, as their disease progresses or becomes resistant to standard-of-care JAK inhibitor treatment.

The Phase I/II trial is part of a comprehensive development program evaluating next-generation PI3Kδ inhibitor roginolisib's tolerability and anti-tumor response across a number of solid and hematologic malignancies.

“Based on non-clinical data being presented at ASH, we anticipate that targeting both the PI3Kδ and JAK pathways could have a synergistic effect in MF — an approach that has previously eluded older generation PI3Kδ inhibitors because of their unfavorable tolerability profiles.” said **Dr Michael Lahn, Chief Medical Officer of iOnctura**.

Overactivation of the PI3K-Akt signaling pathway contributes to the occurrence and progression of cancer[1]. In MF, pathway activation is a well described mechanism of resistance in response to JAK inhibition[2]. Inhibition

[1] He et al., 2021
[2] Moyo et al., 2023

of this pathway using roginolisib may overcome the lack of response and lead to a beneficial therapeutic effect. Non-clinical evidence in support of this mechanism is being presented at ASH on Monday, December 8, 2025 at 6pm EST.

These data demonstrate monotherapy activity of roginolisib against MF cell lines and *in vitro* models of primary MF cells. Further, roginolisib and JAK inhibition (ruxolitinib or momelotinib) exerts a synergistic anti-cancer effect. These data support the rationale behind the ongoing HEMA-MED clinical trial.

Professor Alessandro Vannucchi, Professor of Hematology and Department Head of the Center for Research and Innovation in Myeloproliferative Neoplasms (CRIMM) at the University of Florence, Florence, Italy and Principal Investigator of the HEMA-MED study said: "Myelofibrosis patients often have suboptimal responses to ruxolitinib and/or acquire resistance over time. Roginolisib's intriguing mechanism of action and favorable toxicity profile position it as a compelling partner for ruxolitinib. By combining these agents, we could unlock more durable responses and redefine therapeutic expectations for this challenging rare disease."

In addition to the two posters related to MF, trials in progress posters for the ongoing investigations of roginolisib in peripheral T-cell lymphoma and chronic lymphocytic leukemia (CLL) will also be presented at ASH.

iOnctura poster presentations at the 67th ASH Annual Meeting in Orlando, Florida, USA:

1. A Vannucchi et al. Trial in progress: Sunday, December 7, 06:00 PM - 08:00 PM EST

Abstract 25-4153: A study of roginolisib in combination with ruxolitinib in patients with myelofibrosis who are unresponsive to JAK inhibitors (HEMA-MED)

2. M Balliu et al.: Monday, December 8, 06:00 PM - 08:00 PM EST

Abstract 25-7102: The selective PI3Kd inhibitor roginolisib synergizes with ruxolitinib against progenitor cells from naïve and JAK-inhibitor-refractory/resistant patients with myelofibrosis

3. D Sibon et al. Trial in progress: Sunday, December 7, 06:00 PM - 08:00 PM EST

Abstract 25-11050: PlatTform: A multicenter, multi-arm, academic platform trial evaluating novel agents and combinations in relapsed or refractory peripheral T-cell lymphomas

4. J Brown et al. Trial in progress: Sunday, December 7, 06:00 PM - 08:00 PM EST

Abstract 25-7765: Roginolisib (IOA-244), an orally bioavailable, selective PI3Kδ inhibitor, in combination with venetoclax and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL)

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For more information contact:
Corporate Press Office:
press@iOnctura.com

About myelofibrosis (MF)

MF is a rare myeloproliferative neoplasm marked by activation and growth of mutated cells in the bone marrow, with approximately 0.5 cases per 100,000 individuals diagnosed globally a year[3].

JAK inhibitors are a key treatment option for MF patients and improve symptoms and quality of life, but approximately half of patients discontinue therapy within three years[4]. Reasons for discontinuation include disease progression, tolerability and adverse events and death resulting from resistance to the JAK therapy[5,6].

About the HEMA-MED clinical trial

The HEMA-MED trial (NCT06887803) is a prospective, multi-center, open-label Phase I/II single arm trial consisting of two parts. Part 1 (Phase 1) will enroll 13 patients to assess the safety of the combination of the PI3Kδ inhibitor roginolisib in combination with the JAK inhibitor ruxolitinib, and Part 2 (Phase 2) will expand to enroll 13 additional patients to further allow the assessment of benefit/risk for all 26 patients. In addition to safety, the secondary endpoints of the HEMA-MED trial include blood biomarker and spleen reduction responses, and improvements of MF related symptoms. Exploratory measures will assess endpoints associated with the mechanism of action (MOA) of roginolisib.

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 a non-ATP competitive, allosteric modulator of PI3Kδ with a unique chemical structure and binding mode. Allosteric modulation is a new archetype for precise inhibition of PI3Kδ, promising 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 first-in-class, non-ATP competitive, allosteric modulator of PI3Kδ with a unique chemical structure and binding mode. Allosteric modulation is a new archetype for precise inhibition of PI3Kδ, promising 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

[3] Titmarsh et al., 2014
[4] Verstovsek et al., 2015
[5] Kuykendall et al., 2018
[6] Newberry et al., 2017

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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 program to allow full development in uveal melanoma, while in parallel validating the program in larger market indications.

The Phase II OCULE-01 study in uveal melanoma started in March 2025, the PULMO-01 study in non-small cell lung cancer (NSCLC) started in May 2025 and the HEMA-MED Phase I/II study in myelofibrosis began in November 2025.