New research highlights potential of iOnctura strategy combining autotaxin and TGF-β inhibitors in cancer

Amsterdam, The Netherlands and Geneva, Switzerland, 19 October 2023 - iOnctura, a clinical-stage biotech developing selective cancer therapies against targets that play critical roles in multiple tumor survival pathways, today announces publication of new research data in the peer-reviewed journal *Cancer Research*, that supports a strategy of combining autotaxin inhibitor IOA-289 with TGF-β pathway inhibitor IOA-359.

The research, generated in collaboration with the lab of Professor Davide Melisi, Associate Professor of Medical Oncology at the Department of Medicine, University of Verona, uncovers a central role for autotaxin in resistance to TGF-β pathway inhibition. The TGF-β pathway plays a critical role in promoting tumor aggressiveness, immune escape and resistance to therapy, which has made it an attractive target for cancer therapy. Previous attempts to interrupt TGF-β pathway signaling in cancer have been thwarted by activation of alternative resistance pathways by the tumor. By characterising these resistance mechanisms, iOnctura is designing novel, safe combination treatments that promise to override resistance.

Professor Davide Melisi said: *"We have uncovered a new mechanism of action for autotaxin in resistance to TGF-β pathway inhibition. Data generated by our laboratory across in vitro and in vivo models and from human clinical samples support this important finding. These findings pave the way for clinical studies combining autotaxin inhibitors with TGF-β pathway inhibitors, addressing the fibrotic barrier that protects tumors and reversing immunosuppressive mechanisms encouraging the immune system to mount an attack against cancer cells."*

Catherine Pickering, Chief Executive Officer of iOnctura, said: *"These data support the clinical development of autotaxin inhibitors in combination with TGF-β inhibitors and standard of care for the treatment of pancreatic cancer. This validates our strategy of combining IOA-289, iOnctura's clinical stage autotaxin inhibitor, with IOA-359, our TGF-β inhibitor that we are preparing for clinical development."*

The published research showed that blocking the TGF-β pathway *in vivo* or in *in vitro* co-culture models increased the number of autotaxin-producing inflammatory cancer associated fibroblasts (iCAFs). The autotaxin enzyme in turn increased lysophosphatidic acid (LPA) NF- κB signaling in tumor cells which triggered treatment resistance. Specifically, NF-kB promoted CXCL1 expression and recruitment of myeloid suppressive cells (MDSCs), that limited CD8 T-cell infiltration. Adding the autotaxin inhibitor IOA-289 to TGF-β pathway inhibitor galunisertib and standard of care in PDAC-bearing mice, suppressed NF-κB signaling, reduced MDSC and increased CD8 T-cell infiltration, resulting in prolonged overall survival and curing 40% of the mice.

Most importantly, pancreatic ductal adenocarcinoma (PDAC) patients treated with galunisertib from the H9H-MC-JBAJ trial, had significantly elevated levels of autotaxin compared to patients in the control arm. Median progression free survival was shorter for those with higher autotaxin levels compared to those with lower.

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For more information contact:

iOnctura
Catherine Pickering
Chief Executive Officer
T : +41 79 952 72 52
E: c.pickering@iOnctura.com

Optimum Strategic Communications
Richard Staines / Vici Rabbetts / Elena Bates
T: +44 208 078 4357
E: ionctura@optimumcomms.com

About iOnctura

iOnctura is a clinical-stage biotech developing selective cancer therapies against targets that play critical roles in multiple tumor survival pathways such as cellular proliferation; escape from immune detection; and drug resistance. iOnctura's pioneering approach to drug development is expected to offer significant clinical benefits over the traditional approach of targeting a single pathway alone. iOnctura has progressed two therapeutic candidates into mid-stage clinical development: Roginolisib (IOA-244), a first-in-class allosteric modulator of PI3Kδ; and IOA-289, a highly-selective, non-competitive autotaxin (ATX) inhibitor. IOA-359, a TGF-β pathway inhibitor is also undergoing an extensive pre-clinical program in preparation for first-in-human studies. iOnctura is backed by specialist institutional investors including M Ventures, Inkef Capital, VI Partners, Schroders Capital, and 3B Future Health Fund. iOnctura BV is headquartered in Amsterdam, The Netherlands with its wholly owned Swiss subsidiary, iOnctura SA, located in Geneva, Switzerland.

About IOA-289

IOA-289 is an orally dosed molecule that has shown preclinically to inhibit the growth and proliferation of cancer cells, stimulate immune cell infiltration into tumours and inhibit the development of fibrosis. IOA-289 is being developed as a first-in-class therapy for highly fibrotic cancer indications that overexpress ATX including pancreatic, liver, colorectal, ovarian and breast cancers. A Phase 1b study of IOA-289 in combination with chemotherapy in metastatic pancreatic cancer started in Q4 2022 (NCT05586516).

About IOA-359

IOA-359 is a novel oral TGF-β pathway inhibitor that will be evaluated in solid tumors. Activation of the TGF-β signaling pathway in tumors correlates with tumor aggressiveness, immune escape and resistance to therapy, making it an attractive target for cancer therapy. The inhibition of TGF-β signaling with IOA-359 is expected to attenuate cancer progression through direct effects on cancer, immune and stromal cells. By characterising the resistance mechanisms that typically arise when targeting the TGF-β pathway alone, iOnctura's data-driven precision oncology methods are being used to design novel combination treatments that promise to override tumor survival pathways.