#453P - Proteomic evidence of on-target activity of cambritaxestat (IOA-289) in patients with metastatic pancreatic ductal adenocarcinoma

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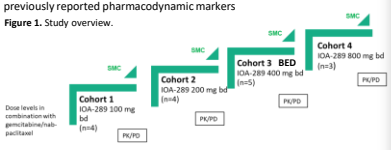
Background

Autotaxin (ATX/ENPP2), a key enzyme producing lysophosphatidic acid (LPA), is overexpressed in metastatic pancreatic ductal adenocarcinoma (mPDAC) and contributes to its fibrotic, immunosuppressive tumor microenvironment. The ATX inhibitor cambritaxestat (IOA-289) was investigated in a Phase I single-arm study in patients with mPDAC in combination with standard-of-care gemcitabine + nab-paclitaxel (SoC) (NCT05586516; Quinzii et al., ESMO 2025- DOI: 10.1016/j.annonc.2025.08.2844). In this study biomarkers of response to IOA-289 were investigated using proteomic profiling in addition to previously reported pharmacodynamic markers

Figure 1. Study overview.



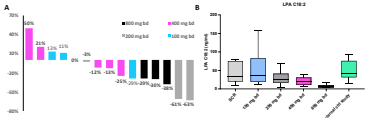
BED, Biologically Effective Dose; PK, pharmacokinetics; PD, pharmacodynamics; SMC, Safety Monitoring Committee

Treatment efficacy

(Quinzii et al., ESMO 2025- DOI: 10.1016/j.annonc.2025.08.2844).

In the Phase I Study (IOA-289-102), 10 out of 15 evaluable patients showed a reduction in target lesions as per the investigator's assessment. Furthermore, continuous dosing of IOA-289 shows a dose dependent PKPD modulation resulting in a sustained reduction of the pharmacodynamic marker LPA C18:2 over time.

Figure 2. A Waterfall Plot - Best Change from Baseline in Sum of Target Lesions. **B** LPA C18:2 levels per cohort for patients at screening (SCR) or receiving IOA-289 in comparison with an external control study receiving SoC only.



Note: In our analysis, we consider all patients with a decrease ≥29% in sum of target lesions as responder and patients with a decrease <29% as a non-responder.

Acknowledgements and Conflict of Interest

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Method Overview

- Normalised proteomics data - Olink® Explore HT platform (5416 proteins).
- Single-arm trial. External control samples taken from an independent Biomarker Study (BIOMARKER STUDY-02). Non-disease protein profiles obtained from healthy volunteer plasma samples.
- Differential expression analysis using Welch's t-test and effect size. Statistical methods such as ANOVA and linear mixed-effects models with false discovery rate correction to model longitudinal proteomic changes.
- Dose- and response-based analyses with pathway enrichment analysis.

Table 1. Study design

Cohort	Sample Size	Treatment	Dosage
Healthy Volunteers	24 patients → 24 plasma samples	None	None
IOA-289-102	16 PDAC patients → 72 plasma samples	IOA-289 (cambritaxestat) + gemcitabine/nab-paclitaxel	100mg, 200mg, 400mg, and 800mg. IOA-289 monotherapy twice daily for 7 days followed by combination therapy for six 28-day cycles.
IOA-Biomarker Study-02	14 PDAC patients → 28 plasma samples	gemcitabine/nab-paclitaxel	Administered in accordance with SmPC.

mPDAC patients show proteomic dysregulation enriched for inflammatory, epithelial–mesenchymal transition (EMT), and wound healing pathways

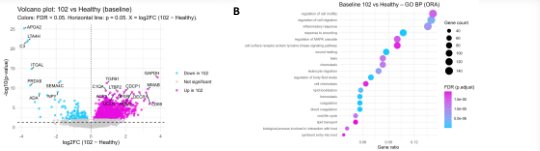

Figure 3. A Differential expression analysis of baseline mPDAC samples against healthy volunteers identified 1,067 proteins that were differentially expressed in mPDAC patients, of which 949 were upregulated and 118 were downregulated relative to healthy controls. **B** Pathway enrichment analysis of these proteins revealed significantly enriched pathways involved in cell motility and migration, inflammatory responses, EMT, cell proliferation, and wound healing. These pathways have previously been reported as key contributors to PDAC pathophysiology.

Treatment with IOA-289 in combination with SoC significantly modulated 350 proteins, compared with 73 proteins modulated by SoC alone

Figure 4. A Longitudinal trend analysis using linear mixed effects model and ANOVA F-test for robustness revealed 350 proteins as differentially regulated over time in patients from IOA-289-102 study, including 326 upregulated and 24 downregulated proteins (**Fig. 4A**). In the Biomarker Study (SoC only), 73 proteins were differentially regulated across time, with 67 upregulated and 6 downregulated. **B** Gene Ontology (GO) pathway enrichment analysis revealed enrichment of pathways associated with extra-cellular matrix remodelling and immune responses in the IOA-289-treated cohort, whereas the SoC-only cohort shows enrichment only for pathways associated with immune responses (**Fig. 4B**). This is a differentiating factor that also provides supporting evidence of IOA-289's mechanism of action .

Proteins linked to cancer microenvironment, fibrosis, EMT and poor prognosis are either down-regulated or stabilized over time in the IOA-289-102 study compared to SoC only cohort

Table 2. Description of proteins exclusively and beneficially modulated by IOA-289.

Protein	Role	PDAC / Cancer Relevance
COL3A1	Fibrillar collagen in ECM, fibroblast / stromal product	Overexpressed in PDAC stroma; linked to desmoplasia, stiff matrix, worse prognosis and immune exclusion.
MMP9	Matrix metalloproteinase that degrades ECM	Upregulated in PDAC; associated with invasion, metastasis, and studied as a biomarker.
GAS6	Ligand for AXL/MERTK/TYRO3 TAM receptors	Promotes survival, EMT, invasion, and resistance; correlates with aggressive behavior.
EPHB4	Receptor tyrosine kinase involved in angiogenesis and migration	Linked to angiogenesis and poor outcomes in PDAC.
ITGAM (CD11b)	Integrin αM; myeloid marker	Key in macrophage and MDSC recruitment; targeting can improve therapy response.

- To discover proteins that behave differently in the IOA-289-102 study compared to the Biomarker study and which might be specifically modulated by ATX inhibition, we selected the proteins that had opposite slopes in both study while being significant for a least one of the two studies.
- 31 proteins were identified meeting those criteria of which 5 proteins were marked as proteins of interest given their role in PDAC cancer: COL3A1, MMP9, GAS6, EPHB4, ITGAM (CD11b). These proteins were downregulated overtime by IOA-289 and stable or upregulated by SoC.

Stratifying the data by dose reveals KRT19 and AGR2 as potential biomarkers with reference to healthy volunteers

- 110 proteins showed differential expression at baseline with effect size >= 2 in PDAC pts compared to HV.
- 94 of these proteins were found to be trending towards healthy values across all doses.
- KRT19 and AGR2 showed largest changes towards healthy at 800 mg of IOA-289, and MPIG6B at 400mg.
- Pathway enrichment of all 94 proteins showed enrichment in pathways related to fibrosis EMT and Oxidative Phosphorylation.

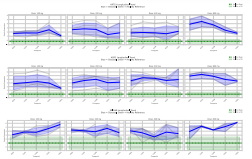

Figure 5. Longitudinal expression of KRT19, AGR2, and MPIG6B in IOA-289-102 stratified by dose. The mean expression for the protein with 95% CI is depicted in green for healthy, and in blue for PDAC.

400 mg of IOA-289 had the largest number of proteins up-/down-regulated towards healthy values

- The overall average changes in expression, and proportion of proteins moving towards healthy, identified 400 mg as a possible optimal dosing strategy.
- 54 out of 110 proteins were moving towards healthy levels at this dose, compared to 47 proteins moving towards healthy at 800 mg.
- The overall change in all 110 proteins as computed by overall mean slope is -0.021698 indicating that the average trend of all the 110 proteins considered is converging towards healthy levels, whereas at the 800 mg dose, the mean slope is 0.078456, indicating slight divergence.

KRT19 and AGR2 are exclusively down-regulated in responders treated with IOA-289 combined with SoC

- Evaluation of protein expression over time in patients between responders and non-responders* identified KRT19 and AGR2 as proteins down-regulated towards healthy at a faster rate in responders*.
- We repeated the analysis on the Biomarker Study data where patients were treated with SoC only.
- SoC only treatment resulted in only 22 proteins modulated towards healthy values in contrast to 94 by IOA-289 combined with SoC.
- KRT19 and AGR2 were absent from this list, indicating exclusivity to the IOA-289-102 study.

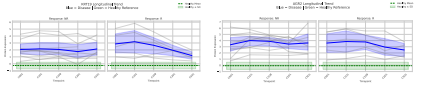

Figure 6. Longitudinal NPX expression of KRT19, and AGR2 in IOA-289-102 study (IOA-289+SoC) stratified by response. The mean expression for the protein with 95% CI is depicted in green for healthy, and in blue for PDAC.

*Note: In our analysis, we consider all patients with a decrease ≥29% in sum of target lesions as responder and patients with a decrease <29% as a non-responder.

Conclusion

Proteomic analysis of plasma samples from patients treated with IOA-289 in combination with SoC treatment reveals changes in known key biomarkers of PDAC. These findings provide mechanistic support for ATX inhibition, identify candidate pharmacodynamic biomarkers, and inform dose selection, thus supporting further clinical development of IOA-289 against tumours characterized by fibrosis. An investigation into other indications that could benefit from ATX inhibition resulted in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CHOL) as top hits. From TCGA data, KRT19 was found to be significantly upregulated in tumour samples compared to normal in CHOL, and KRT19 and AGR2 were found to be significantly positively correlated with ENPP2 in samples with high ENPP2 expression in HCC.