200P: Patient tumour profiling supports the antitumour activity of the autotaxin inhibitor cambritaxestat (IOA-289) as monotherapy and in combination with standard of care in hepatocellular carcinoma and cholangiocarcinoma.

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Abstract

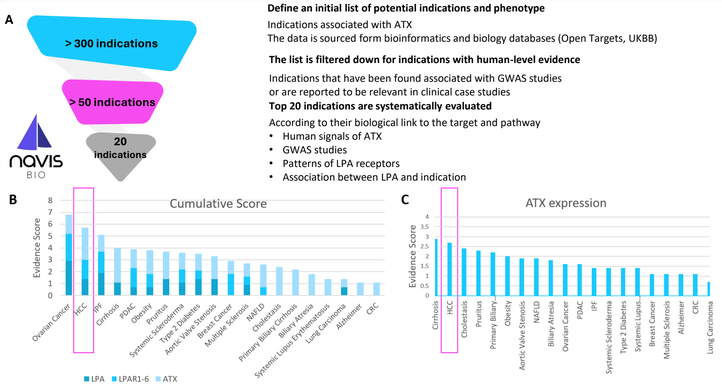
Background

Autotaxin (ATX) drives stromal remodeling, fibrosis, and immune suppression in solid tumours. Cambritaxestat (IOA-289) is an oral, selective ATX inhibitor. An AI-driven reverse translational framework prioritised hepatocellular carcinoma (HCC) as a leading indication for ATX targeting. We further evaluated ATX expression and cambritaxestat activity in human HCC and cholangiocarcinoma (CC) using complementary translational platforms benchmarked against standard of care (SoC).

Results

AI analysis identified HCC as the top candidate indication. ATX expression was quantified in HCC tumouroids, and five ATX-high models were selected for tumour cell killing assays. Cambritaxestat was tested as monotherapy or combined with bevacizumab plus durvalumab (standard of care (SoC) and compared with SoC alone; tumour cell death was assessed by confocal imaging. In ATX-high HCC tumouroids, cambritaxestat monotherapy induced tumour cell death in 80% (4/5) of models, compared with 60% (3/5) for SoC. Combination therapy achieved responses in 80% (4/5) of models. In an independent platform, combination treatment was predicted to outperform SoC across all HCC samples (4/4), while cambritaxestat monotherapy reached response thresholds in 50% (2/4). In CC, combination therapy induced responses in 60% (3/5) versus 20% (1/5) in SoC alone.

1. AI-Driven approach identifies HCC as top indication candidate based on known literature



Define an initial list of potential indications and phenotype

Indications associated with ATX
The data is sourced form bioinformatics and biology databases (Open Targets, UKBB)

The list is filtered down for indications with human-level evidence

Indications that have been found associated with GWAS studies
or are reported to be relevant in clinical case studies

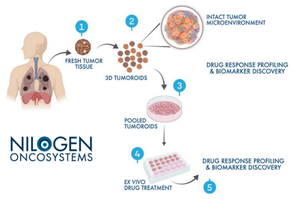
Top 20 indications are systematically evaluated

According to their biological link to the target and pathway

- Human signals of ATX
- GWAS studies
- Patterns of LPA receptors
- Association between LPA and indication

A Schematic description of the analysis funnel. **B** Cumulative Evidence Score of LPA, LPAR and ATX scores for the top 20 indication. **C** ATX Expression Score for the the 20 indications.

4. Cambritaxestat (IOA-298) mono- and combination therapy induce tumour cell death in human HCC tumouroids



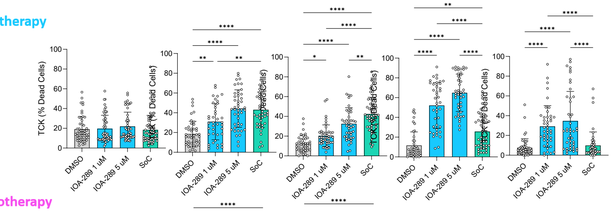
B

Monotherapy or in combo with SOC:
HCC -> Bevacizumab (aVEGF) + Durvalumab (aPDL1)

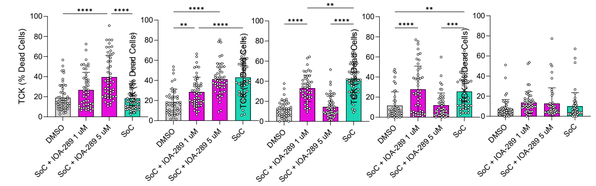
Tumor Site	Histologic Type	Grade	Stage
Liver	Hepatocellular carcinoma	G2	pT2 pN0

ID	% of ATX+ cells	ATX H-score
HCC2	73.59	95.39
HCC3	65.31	71.3
HCC4	70.24	76.76
HCC6	31.68	36.14
HCC7	38.34	40.82

C Monotherapy

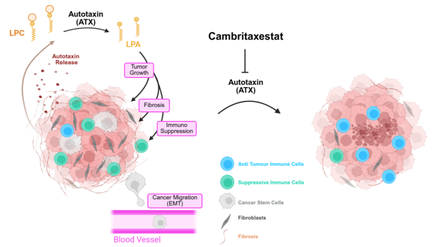


D Combotherapy

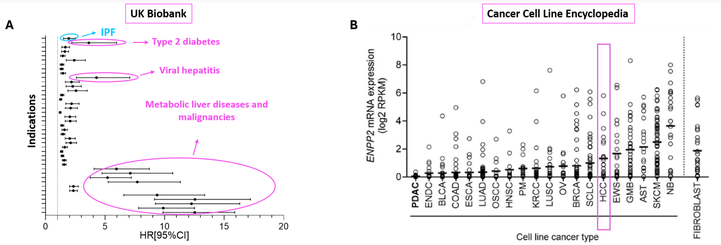


A Schematic description of sample processing and analysis. **B** Therapies used and pathology information on the cancer type; autotaxin staining levels for tumouroids selection. Viability assay of IOA-289 treatment in **C** monotherapy or in **D** combotherapy with SoC. Each dot is a technical replicate and each plot is am individual tumouroid from a patient.

Cambritaxestat Mechanism of Action

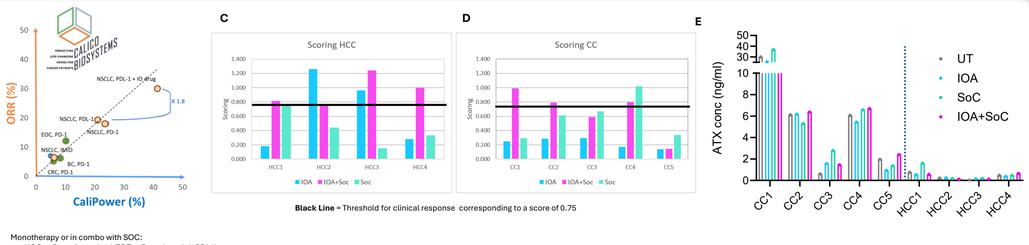


2. Public dataset and Biobanks analyses support a rationale to focus on liver indications



A Protein-wide association analysis (UK Biobank Pharma Proteomics Project), showed significant ENPP2 (ATX gene) expression in 209 diseases, with the liver indications ranking highest. **B** ENPP2 (ATX) expression in cancer cell lines extracted from the Cancer Cell Line Encyclopedia.

5. Cambritaxestat is predicted to improve SoC efficacy in HCC and iCCA in human tumours



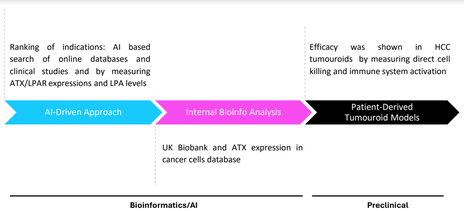
Black Line = Threshold for clinical response corresponding to a score of 0.75

B

Monotherapy or in combo with SOC:
- HCC -> Bevacizumab (aVEGF) + Durvalumab (aPDL1)
- CC -> Chemotherapy + Durvalumab

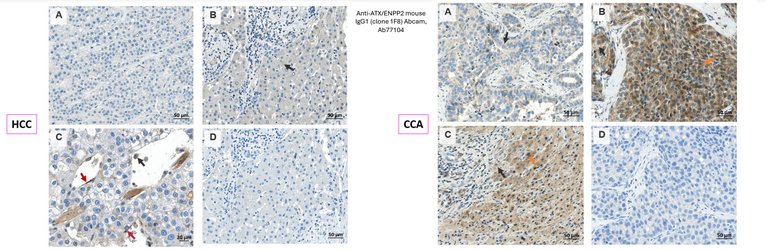
A Correlation between CaliPower Score and overall response rate (ORR) to predict clinical efficacy. **B** Treatments used for the experiment as SoC. **C** CaliPower Score for IOA-289 monotherapy, in combination with SoC or SoC alone. In **C** HCC C and in **D** CCA. **E** ELISA to measure ATX concentration levels in the tumouroids at baseline.

Conclusion



Across independent human tumouroid platforms, cambritaxestat demonstrated antitumour activity as monotherapy in HCC and enhanced efficacy in combination with SoC in both HCC and CC. These findings support further clinical development of ATX inhibition in liver cancers.

3. Optimized anti-ATX/ENPP2 IHC staining of human hepatocellular carcinoma tissue and Cholangiocarcinoma tissue



Anti-ATX/ENPP2 IHC of FFPE HCC tissue. A No cytoplasmic anti-Atx/ENPP2 staining of tumour cells was detected in HCC sample. **B** Normal hepatocytes exhibited a weak anti-ATX/ENPP2 staining (black arrow) in HCC sample. **C** A weak cytoplasmic anti-TX/ENPP2 in immune cells (black arrow) and a strong cytoplasmic anti-ATX/ENPP2 in endothelial cells (red arrows) was detected in HCC sample. **D** The corresponding isotype control was negative for HCC sample.

Anti-ATX/ENPP2 IHC of FFPE CCC tissue. A A weak cytoplasmic anti-ATX/ENPP2 staining was detected in CCC sample (H-score: 15). **B** A weak (black arrow) to moderate (orange arrow) cytoplasmic anti-ATX/ENPP2 staining of tumour cells was detected in CCC sample (H-score: 185). **C** A weak (black arrow) to moderate (orange arrow) anti-ATX/ENPP2 staining was detected in normal hepatocytes of CCC sample. **D** The corresponding isotype control was negative for CCC sample.

6. Two independent preclinical models performed in human HCC tumouroids show consistent cambritaxestat response in monotherapy or in combination with SoC

A Nilogen Oncosystems

HCC:

IOA-289 monotherapy induces tumor cell death in 4/5 (80%) of HCC tumouroids

IOA-289 monotherapy performs equally or better than SoC in 4/5 (80%) of HCC tumouroids

Combo therapy induces tumor cell death in 4/5 (80%) of HCC tumouroids

Combo therapy performs equally or better than SoC in 4/5 (80%) of HCC tumouroids

SoC induces tumor cell death in 3/5 (60%) of HCC tumouroids

B Calico Biosystems

HCC:

Only 1/4 sample show response for SoC (comparable to clinic ~20%)

Combo is predicted to have a clinical response and outperform SoC in 4/4 (100%) samples

IOA-289 Monotherapy is predicted to have a clin resp and outperform SoC in 2/4 (50%) samples

IOA-289 Monotherapy is predicted to have a clin resp and outperform Combo and SoC in 1/4 (25%)

CCA:

Only 1/5 sample show response for SoC (comparable to clinic ~20%)

Combo is predicted to have a clinical response in 3/5 (60%) samples

IOA-289 Monotherapy is predicted to not reach clinical response

C Comparison HCC

	Nilogen Oncosystems	Calico Biosystems
Sample selection by ATX expression	Yes, over 30% expression by IHC	No
Readout	Direct tumor cell killing → intrinsic	Immune microenvironment parameters → extrinsic
IOA-289 monotherapy	4/5 responders (80%)	2/4 responders (50%)
IOA-289 + SoC	4/5 responders (80%)	4/4 responders (100%)
SoC	3/5 responders (60%)	1/4 responders (25%)

A Table recapitulating the response rate results of figure 4. **B** Table recapitulating the response rate results of figure 5.
C Table comparing the data from the two different preclinical models for HCC.

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