Abstract #2227P: Safety and clinical efficacy of cambritaxestat (IOA-289), a novel autotaxin inhibitor, plus gemcitabine and nab-paclitaxel (GnP) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC)

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BACKGROUND

Autotaxin (ATX) is a key mediator of fibrosis, inflammation and therapeutic resistance across multiple malignancies. Cambritaxestat (IOA-289) is a first-in-class oral ATX inhibitor with demonstrated anti-fibrotic, immune-enhancing and anti-tumour activity. Pancreatic ductal adenocarcinoma (PDAC) is known to be embedded in a dense fibrotic tumour microenvironment (TME) which is a crucial factor that influences development, progression, metastasis, and resistance to treatment. Cambritaxestat could enhance the anti-tumor activity of standard of care cytotoxic therapy in metastatic PDAC.

OBJECTIVES

Primary:

Safety and tolerability of escalating doses of cambritaxestat in combination with standard chemotherapy consisting of gemcitabine and nab-paclitaxel

Secondary:

- To determine the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of cambritaxestat
- To define the biologically effective dose (BED) of cambritaxestat
- To assess changes of CA19-9 levels compared to baseline
- To determine the PD activity of cambritaxestat, including reduction of LPA C18:2 levels
- Document preliminary efficacy of cambritaxestat e.g., overall response rate (ORR), duration of response (DoR), progression free survival (PFS) and overall survival (OS)

Exploratory:

- To determine the effect of cambritaxestat on blood and tissue-based biomarkers.

METHODS

Design: 3+3 cohort dose escalation

7-day BID cambritaxestat monotherapy lead-in followed by BID cambritaxestat in combination with gemcitabine (1000 mg/m2) and nab-paclitaxel (125 mg/m2) both administered IV on days 1,8 and 15 of a 28-days cycle.

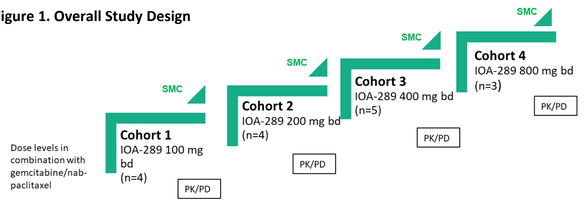
Patients Eligibility:

- ≥18 years of age with the following:
- Performance status of 0-1 on the ECOG scale
- Histological or cytological evidence of metastatic pancreatic adenocarcinoma
- No prior systemic anti-cancer therapy for metastatic pancreatic cancer
- Adequate organ functioning

Assessments:

- Toxicities graded to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- Standard laboratory hematology and chemistry
- RECIST V1.1. based evaluations
- CA19-9, LPA C18:2 and ATX levels in blood (baseline and on treatment)

Figure 1. Overall Study Design



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

BASELINE CHARACTERISTICS

Sixteen patients received cambritaxestat BID at doses of 100 mg (n=4), 200 mg (n=4), 400 mg (n=5) and 800 mg (n=3).

Table 1. Demography and Baseline Characteristics

Cohort (IOA-289 dose)	1 (100 mg bd)	2 (200 mg bd)	3 (400 mg bd)	4 (800 mg bd)	Overall
N	**4**	**4**	**5**	**3**	**16**
Median Age (range)	63 (54-66)	69 (60-71)	65 (61-75)	54 (51-70)	65 (51-75)
Sex (m/f)	2/2	2/2	3/2	1/2	8/8
Stage at trial entry					
IV	4	4	5	3	16
ECOG at Screening (%)					
0	3 (75%)	4 (100%)	5 (100%)	2 (67%)	14 (88%)
1	1 (25%)	0	0	1 (33%)	2 (12%)
Liver Mets present					
At screening	2 (50%)	4 (100%)	4 (80%)	2 (67%)	12 (75%)
Target lesions	2 (50%)	4 (100%)	4 (80%)	2 (67%)	12 (75%)
Non-target lesions	2 (50%)	3 (75%)	3 (60%)	2 (67%)	10 (63%)

Source: Table 14.1.2.1, 14.1.2.2 Final TFLs

CAMBRITAXESTAT SAFE AND TOLERABLE

Table 2. All Cause and Drug Related TEAEs

	Cohort 1 (100 mg bd) n=4			Cohort 2 (200 mg bd) n=4			Cohort 3 (400 mg bd) n=5			Cohort 4 (800 mg bd) n=3			Overall n=16		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
All Causality TEAEs															
Any Grade	4	(100 %)	111	4	(100 %)	79	5	(100 %)	118	3	(100 %)	43	16	(100.0 %)	351
Grade 1	4	(100 %)	65	4	(100 %)	39	5	(100 %)	61	3	(100 %)	23	16	(100.0 %)	188
Grade 2	4	(100 %)	36	3	(75 %)	28	5	(100 %)	42	3	(100 %)	16	15	(93.8 %)	122
Grade 3	4	(100 %)	9	3	(75 %)	7	5	(100 %)	14	2	(67 %)	4	14	(87.5 %)	34
Grade 4	1	(25 %)	1	2	(50 %)	5	1	(20 %)	1	0	*	0	4	(25.0 %)	7
Grade 5	0		0	0		0	0		0	0		0	0		0
IOA-289 Drug related TEAEs															
Any Grade	1	(25 %)	2	1	(25 %)	1	0		0	0		0	2	(12.5 %)	3
Grade 1	1	(25 %)	1	1	(25 %)	1	0		0	0		0	2	(12.5 %)	2
Grade 2	1	(25 %)	1	0		0	0		0	0		0	1	(6.3 %)	1
Grade 3	0		0	0		0	0		0	0		0	0		0
Grade 4	0		0	0		0	0		0	0		0	0		0
Grade 5	0		0	0		0	0		0	0		0	0		0

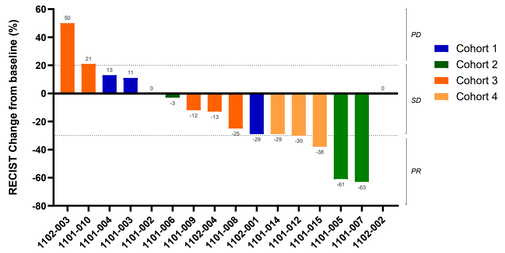
Source: Data extracted from EDC 8 May 25- non-validated and subject to change

No dose-limiting toxicities were reported, and no treatment-emergent adverse events (TEAE) led to drug discontinuation. No serious TEAEs considered related to cambritaxestat were observed and no deaths on treatment were reported.

ANTI-TUMOUR ACTIVITY

Ten out of 15 evaluable patients had a reduction in tumor size as per investigators assessment of target lesions.

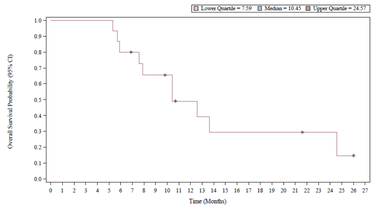
Figure 2. Waterfall Plot - Best Change from Baseline in Sum of Target Lesions



BEST RESPONSE AND OVERALL SURVIVAL

Median duration of treatment was 4.7 (range: 0.7 to 18) months, with one patient remaining on treatment at data cut-off. At the 200 mg dose, confirmed partial response (PR) was observed in 2 of 4 patients (50%) at Cycle 5 and 7. Stable disease (SD) was the best overall response (OR) observed at other dose levels.

Figure 3. Kaplan-Meier Figure of Overall Survival

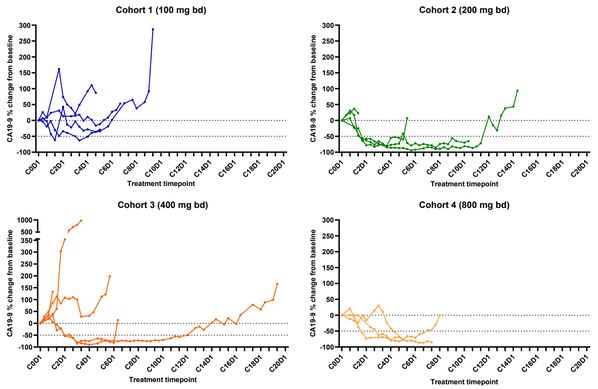


Median overall survival (OS) was 10.4 (range: 5.3 to 26.0) months.

CA19-9 TUMOR MARKER RESPONSE

Tumor marker CA19-9 levels declined from Cycle 2 onward in the 200 mg BID cohort and above, with >50% reductions sustained for more than 4 months.

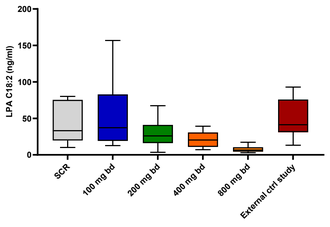
Figure 4. Individual Patients CA19-9 Tumor Marker Response per Cohort



CAMBRITAXESTAT DRIVES LPA C18:2 REDUCTIONS

Continuous dosing of cambritaxestat shows a dose dependent PKPD modulation resulting in sustained LPA C18:2 reduction over time. Data from an external control study show that LPA C18:2 reductions are not seen with chemotherapy alone (Figure 5).

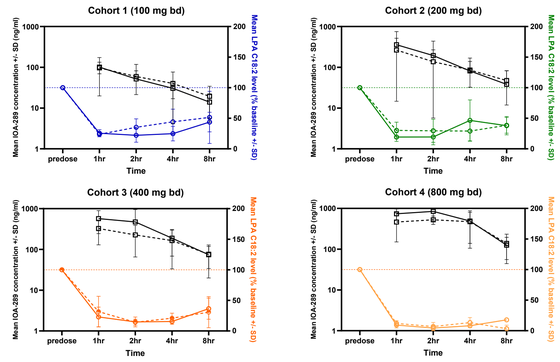
Figure 5. All Reported LPA C18:2 Levels per Cohort for Patients at Screening or Receiving Cambritaxestat versus External Control Study Levels



PHARMACOKINETICS AND PHARMACODYNAMICS

Cambritaxestat shows a dose proportional exposure, moderate to high interpatient variability and half-life of 2-3 hrs. Cambritaxestat shows dose dependent reduction in LPA C18:2 (Figure 5 and 6). A 50% reduction is observed over 24 hrs.

Figure 6. PK/PD Correlation on C0D1 and C1D1 per Cohort



Black solid line: PK on C0D1; black dotted line: PK on C1D1; colored solid lines: LPA C18:2 on C0D1; colored dotted lines: LPA C18:2 on C1D1.

CONCLUSIONS

- **Cambritaxestat is safe and well tolerated in combination with gemcitabine/nab-paclitaxel**
- **Pharmacodynamic (PD) analysis shows dose dependent reduction in plasma LPA C18:2 over 24 hrs**
- **No LPA reduction observed in an external study of mPDAC patients receiving GnP chemotherapy alone**
- **Patients in the higher dose cohorts had consistent and durable CA19-9 reductions**
- **Late onset responses at Cycle 5 and 7 with prior SD were observed**
- **Signs of anti-tumor activity warrant further exploration**

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DISCLOSURES

Dr. Alberto Quinzii has no disclosures.

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