Safety and clinical efficacy of IOA-289, a novel autotaxin inhibitor, plus gemcitabine and nab-paclitaxel (GnP) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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BACKGROUND

Autotaxin (ATX) plays a critical role in inflammation and resistance mechanisms in a wide range of malignancies. IOA-289 is a novel inhibitor of ATX, with anti-fibrotic, immune-enhancing and anti-tumour activity. This first-in-human trial evaluated safety, and preliminary antitumor activity of IOA-289 with GnP in patients with mPDAC

OBJECTIVES

Primary:

- Evaluate safety and tolerability of escalating doses IOA-289 in patients with metastatic pancreatic cancer in combination with standard chemotherapy consisting of gemcitabine and nab-paclitaxel (GnP).

Secondary:

- Pharmacokinetics of IOA-289
- Define the biologically effective dose (BED) of IOA-289
- Assess change in CA19-9 levels compared to baseline
- Determine PD activity of IOA-289 (including LPA C18:2)

METHODS

Design: 3+3 cohort dose escalation
IOA-289 given as continuous twice daily dosing (BID).
IOA-289 initially administered for 7 days as a monotherapy (Cycle 0)
After 7 days, standard GnP is added in 3 weekly schedule with 1 week pause (Cycle 1 onwards)

Patients Eligibility

- ≥18 years of age with the following:
- Performance status of 0-1 on the ECOG scale
- Histological or cytological confirmed metastatic unresectable pancreatic adenocarcinoma
- Eligible for 1st line systemic treatment with GnP for metastatic disease
- Adequate organ functioning

Assessments:

- Toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- Standard laboratory hematology and chemistry
- RECIST 1.1. based evaluation (ORR)
- CA19-9 and blood based PD markers

RESULTS

Demography and Baseline Characteristics

Cohort	100 mg bd	200 mg bd	400 mg bd	Overall
N	4	4	5	13
Median Age (range)	63 (54-66)	69 (60-71)	65 (61-75)	65 (54-75)
Sex (m/f)	2/2	2/2	3/2	7/6
Stage at trial entry				
IV	4	4	5	13
ECOG at Screening (%)				
0	2 (50%)	4 (100%)	4(80%)	10 (77%)
1	2 (50%)	0	1 (20%)	3 (23%)
Liver Mets present				
At screening	2 (50%)	4 (100%)	4 (80%)	10 (77%)
Target lesions	2 (50%)	4 (100%)	4 (80%)	10 (77%)
Non-target lesions	2 (50%)	3 (75%)	3 (60%)	8 (62%)

Patients are representative of PDAC population receiving 1st Line chemotherapy treatment. Most target lesions were located in the liver.

Safety

IOA-289-102 Overall Summary of TEAES by CTC grade - Dose escalation

	Cohort 1 (100 mg bd) n=4			Cohort 2 (200 mg bd) n=4			Cohort 3 (400 mg bd) n=5			Overall n=13		
	n	%	E	n	%	E	n	%	E	n	%	E
All Causality TEAEs												
Any Grade	4	(100 %)	111	4	(100 %)	65	4	(80 %)	71	13	(100.0 %)	247
Grade 1	4	(100 %)	64	4	(100 %)	32	5	(100 %)	31	13	(100.0 %)	127
Grade 2	4	(100 %)	37	3	(75 %)	24	4	(80 %)	30	11	(84.6 %)	91
Grade 3	4	(100 %)	9	3	(75 %)	6	4	(80 %)	9	11	(84.6 %)	24
Grade 4	1	(25 %)	1	2	(50 %)	3	1	(20 %)	1	4	(30.8 %)	5
Grade 5	0		0	0		0				0		0
IOA-289 Drug related TEAEs												
Any Grade	1	(25 %)	2	1	(25 %)	1	0		0	2	(15.4 %)	3
Grade 1	1	(25 %)	1	1	(25 %)	1	0		0	3	(23.1 %)	2
Grade 2	1	(25 %)	1	0		0	0		0	1	(7.7 %)	1
Grade 3	0		0	0		0	0		0	0		0
Grade 4	0		0	0		0	0		0	0		0
Grade 5	0		0	0		0	0		0	0		0

Data extracted from EDC 26Jan24 - non-validated

Adverse Events (AE) summary indicates that IOA-289 does not add to the toxicity profile of Gemcitabine/Nab-Paclitaxel (GnP)

Treatment Modifications

IOA-289-102 Gemcitabine/Nabpaclitaxel Dose Modifcation

Cohort	Cohort 1 n=4			Cohort 2 n=4			Cohort 3 n=5		
	e	n	%	e	n	%	e	n	%
Treatment Interruption	7	3	(75 %)	10	2	(50 %)	7	4	(80 %)
AE	7	3	(75 %)	10	2	(50 %)	5	3	(60 %)
Other (operation)			(0 %)			(0 %)	1	1	(20 %)
Disease progression			(0 %)			(0 %)	1	1	(20 %)
Dose reduction	17	2	(50 %)	13	2	(50 %)	0	0	(0 %)
1 dose level reduction		1	(25 %)		2	(50 %)			(0 %)
2 dose level reductions		2	(50 %)			(0 %)			(0 %)

Data extracted from EDC 26Jan24 - non-validated. Gemcitabine and nab paclitaxel were interrupted or reduced together for all but 1 patient – see below

Most treatment modification for GnP were done in Cohort 1. One dose reduction for IOA-289 (400 mg to 200 mg), which was not considered related to treatment. No dose reductions (including chemotherapy) required at start of each new cycle allowing for optimal chemotherapy delivery (note: one pt had reduction for nab-paclitaxel only at C8 D1)

Figure 1: Serum CA19-9 levels (Central Laboratory) in Patients Treatment with IOA-289 (monotherapy) followed by combination with GnP

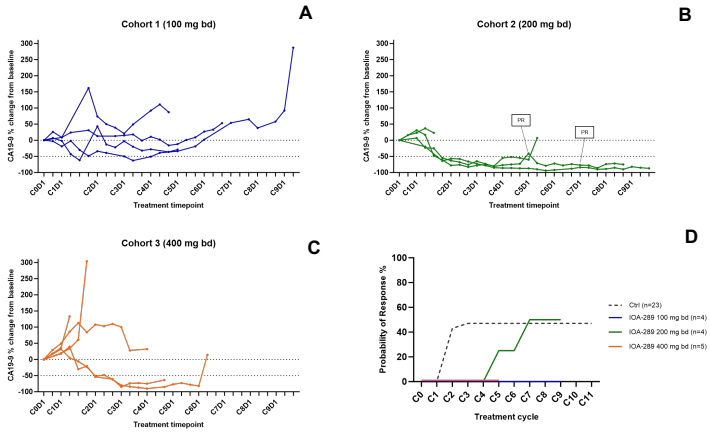

Figure 1: Panels A-C show serum CA19-9 changes from baseline across the 3 dose levels observed. Panel D compares the RECIST 1.1 appearance of first overall response rate of patients enrolled in the present trial to a cohort of patients with similar enrolment criteria conducted at one of the centres participating in this trial.

ORR appear later than expected for GnP chemotherapy and may reflect an alteration of the tumour microenvironment.

Figure 2: Time on Treatment of IOA-289 (7 days monotherapy) and bd dosing in combination with Nab-paclitaxel/gemcitabine (remaining cycles)

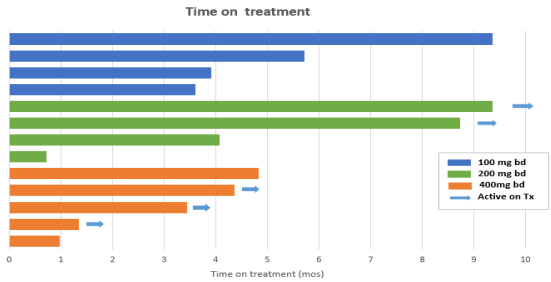

Figure 2: Patients at the 100 mg BID dose level (blue) had a time on treatment comparable to historic data, while patients at the 200 mg BID dose level (green) emerge with longer than expected treatment time. Patients on the 400 mg BID are still on treatment.

CONCLUSIONS

- IOA-289 is well tolerated at 100-400 mg BID dose levels in combination with standard GnP
- Patients in the higher dose Cohorts are experiencing robust CA19-9 reductions consistent with ORR
- To our knowledge, this is the first time an autotaxin inhibitor has been investigated in cancer patients

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