A first-in-human phase I study of IPH5301, an anti-CD73 monoclonal antibody, in patients with advanced solid tumors (CHANCES, NCT05143970)

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M. Beaufils[1] - A. Mailliez[2] - P. Sfumato[3] - C. Vicier[1,4] - M. Provansal[1] - M. Guérin[1] - B. Chanez[1] - N. Kotecki[4,5] - A. Widemann[6] - S. Panzolato[6] - A. Boyer Chammard[6] - P. André[6] - C. Paturel[6] - C. Gouarne[3] - A. Awada[4,5] - J.M. Boher[3] - A. Gonçalves[1,4,7,8]

1. Medical Oncology Department, Institut Paoli-Calmettes, Marseille, France - 2. Medical Oncology Department, Centre Oscar Lambret, Lille, France - 3. Clinical Research and Innovation, Institut Paoli-Calmettes, Marseille, France - 4. Oncodistinct network - 5. Medical Oncology Department, Institute Jules Bordet, Brussels, Belgium - 6. Innate Pharma, Marseille, France - 7. Aix-Marseille University - 8. Corresponding author (goncalvesa@ipc.unicancer.fr)

BACKGROUND

CD73

• CD73 is an extracellular ectonucleotidase overexpressed in the tumor microenvironment (TME) of multiple cancers (Leone and Emens, 2018).

•Within the TME, extracellular adenosine triphosphate (ATP) released by necrotic cells is hydrolyzed by CD39 extracellular enzyme into adenosine monophosphate (AMP), which is subsequently degraded into adenosine by CD73. Adenosine has immunosuppressive effects and is upregulated in the TME (figure 1A).

•CD73 overexpression has been associated with poor prognosis in several tumor types, including breast and gastric cancer, conferring resistance to chemotherapy and anti-HER2 therapy (Wang et al, 2017).

IPH5301

• IPH5301 is a humanized IgG1 antagonist monoclonal antibody (mab) with a functionally silent Fc domain.

• IPH5301 specifically inhibits both soluble and membrane CD73 enzymatic activity.

•IPH5301 releases TME from adenosine-mediated immune suppression, ultimately restoring activation of T cells (figure 1B), more effectively in preclinical models than other anti-CD73 mAbs in clinical development (Perrot et al., 2019).

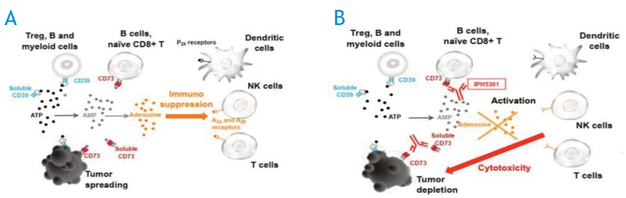


Figure 1: Mechanisms of Actions

METHODS - STUDY DESIGN

A multicentre, first-in-human, phase I study enrolling up to 15 patients in the escalation part of selected cancer types to define RP2D of IPH5301 as single agent using a modified continual reassessment method (CRM, O'Quick- ley et al., Biometrics 1990).

Main eligibility criteria:

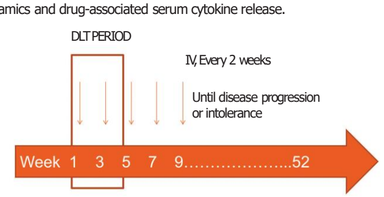
- Prior treatment with at least one prior systemic therapy in the advanced metastatic setting.
- Selected tumor types :breast, gastric, oesophageal, pancreatic, lung, endometrium or ovarian cancers considered as failing standard therapeutic alternatives and candidate to a phase I study by a multi-disciplinary tumor board.
- ECOG-OMS PS 0-1.
- Measurable disease according to RECIST1.1.
- Adequate liver, renal and hematological function.

Objectives:

- Primary = to determine the *maximum tolerated dose (MTD) of IPH5301 alone.*
- Secondary = to evaluate pharmacokinetics, preliminary clinical activity, immunogenicity of IPH5301.
- Exploratory = blood pharmacodynamics and drug-associated serum cytokine release.

Dose level (DL)	nb patients
DL-1, 100 mg	
DL1, 300 mg	n=2
DL2, 900 mg	n=2
DL3, 1500 mg	n=3
DL4, 2400 mg	n=3

Intrapatient escalation was allowed



RESULTS

PATIENTS

As of Jan 2, 2024, IPH5301 was administered to 12 pts during the dose escalation portion (Table 1).

Table 1: Demographic and baseline characteristics

Demographic and baseline characteristics	IPH5301 dose escalation (n=12)
Age, median [range], years	58.50 [35.00-68.00]
Sex, female (%)	12 (100%)
ECOG-OMS PS, n (%) - 0 - 1	 8 (66%) 4 (33%)
Site of primary cancer - Breast - Ovary	 8 (66%) 4 (33%)
Numer of metastatic sites at baseline Median [range]	 2.5 (1-5)
Pretreatment - Number of previous line, median [range] - Chemotherapy n, (%) - Endocrine treatment n, (%) - Targeted treatment n, (%) - Immunohterapy n, (%) - Radiotherapy	 5 (3-10) 12 (100%) 7 (58%) 7 (58%) 1 (8%) 7(58%)

SAFETY

Treatment related adverse events (TRAEs) occurred in 91% of patients, with none being Grade 3/4. No DLT was observed across the 4 dose level explored.

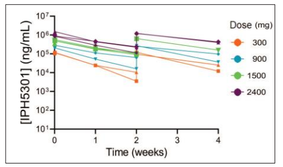
Table 2: Safety overview

Overview adverse events	All patients (n=12)	
	All grades	Grade 3 or+
Patients with at least an adverse event (AE)	12 100%)	3 (25%)
Patients with TRAEs	11 (91%)	0
Patients with serious adverse events (SAE)	3 (25%)	1 (8%)
Patients with treatment related SAE	2 (16%)	0
Patients with AE leading to treatment discontinuation		0
Patients with TRAE leading to tretment discontinuation		0
Patients with AE leading to death		0
Patients with TRAE leading to death		0

Table 3: Most common TRAE

TRAE	All patients (n=12)		DL1, 300 mg (n=3)		DL2, 900 mg (n=2)		DL3, 1500mg (n=3)		DL4, 2400 mg (n=4)	
	All	G3 or+	All	G3 or+	All	G3 or+	All	G3 or+	All	G3 or+
Atrio-ventricular block	1	0	0	0	0	0	1	0	0	0
Photopsia	1	0	1	0	0	0	0	0	0	0
Abdominal pain	2	0	0	0	1	0	1	0	0	0
Constipation	1	0	0	0	1	0	0	0	0	0
Diarrhea	2	0	1	0	1	0	0	0	0	0
Nausea	6	0	2	0	1	0	2	0	1	0
Vomiting	2	0	0	0	0	0	1	0	1	0
Asthenia/fatigue	7	0	2	0	2	0	2	0	1	0
Infusion related reaction	2	0	0	0	0	0	1	0	1	0
Headache	1	0	0	0	0	0	1	0	0	0
Dyspnea	1	0	1	0	0	0	0	0	0	0

PHARMACOKINETICS, IMMUNOGENICITY

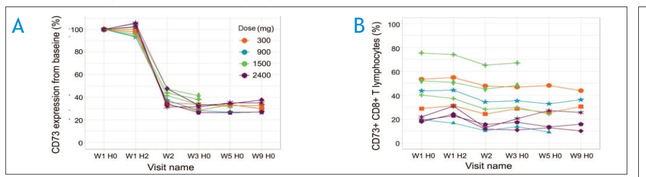


Serum concentration of IPH5301 (ng/mL) versus time. Serum concentration of IPH5301 was evaluated by ELISA (LLOQ= 156.3 ng/mL).
Number of patients:
DL1, 300 mg n=3; DL2, 900 mg, n=2; DL3, 1500 mg, n=3 and DL4, 2400 mg n=4.

IPH5301 concentration was maintained well above 10µg/mL in all patients from DL2 (900mg), with low accumulation (<x2) at repeated dosing, dose proportional PK and half-life between 4-7 days. ADA was detected only, and at low titer, in 1 patient in DL4 at baseline, and 1 patient at DL2 at W9, with no impact on PK,

PHARMACODYNAMICS

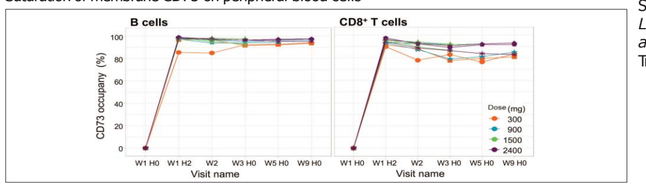
CD73 surface expression and CD73+ peripheral blood subsets



A: Cell surface expression of CD73 was assesssed by flow cytometry (measure of CD73 mean fluorescence intensity on CD8+ T cells in comparison to baseline). Similar results were obtained on B cells.
B: CD73+CD8+ T cells (among CD8+T cells) were evaluated by flow cytometry on whole blood.

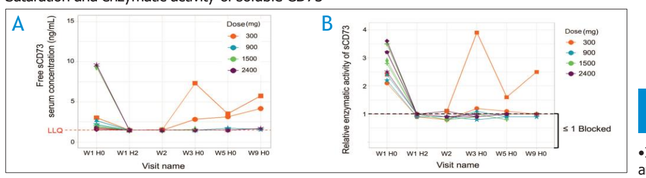
Down-modulation of mb CD73 on peripheral blood cells at all dose levels associated with no major changes of CD73+ peripheral blood subset distribution and no change in cell count.

Saturation of membrane CD73 on peripheral blood cells



Membrane CD73 occupancy was assessed by flow cytometry on whole blood (gating on B lymphocytes and CD8+ T lymphocytes).

Saturation and enzymatic activity of soluble CD73



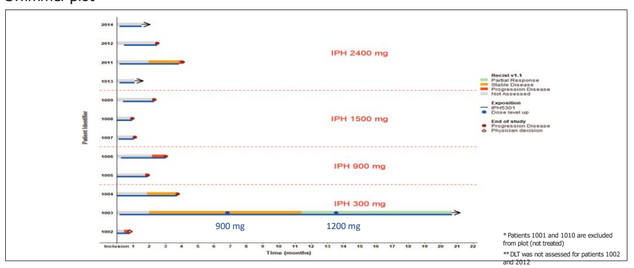
A: Serum concentration of free sCD73 (ELISA, LLOQ= 1.46 ng/mL) versus nominal visit.
B: Comparison of AMPase activity of sCD73 in presence or absence of IPH5301 added ex vivo.
Relative enzymatic activity: >1= sCD73 enzymatic activity is not blocked ; ≤ 1= sCD73 enzymatic activity is blocked

Saturation of membrane and soluble CD73 in peripheral blood, as well as blockade of soluble CD73 enzymatic activity in sera were achieved from DL2 (900 mg).

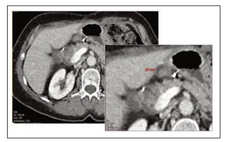
EFFICACY

IPH5301 PLANNED DOSE AT INITIATION (mg)	All DLs (n=12)	DL1 (n=3) 300 mg	DL2 (n=2) 900 mg	DL3 (n=3) 1500 mg	DL4 (n=4) 2400 mg
BEST OVERALL RESPONSE					
- Partial Response	1 (8%)	1	0	0	0
- Stable Disease	4 (33%)	1	0	0	3
- Progressive Disease	7 (59%)	1	2	3	1

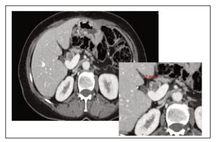
Swimmer plot



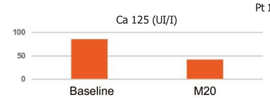
Pt 1003- women 62, BRCA1mut high-grade serous ovarian carcinoma with durable partial response (PR)
Stage III diagnosis on Feb 2014, 5 prior lines
L1 Carbo-taxol x 3 – complete surgery – Carbo-taxol x 3 (2014) L2 Carbo-taxol and then carboplatine alone (2016) L3 Carbo-gemzar olaparib maintenance (2018) L4 Carbo-caelyx (2019) L5 Carbo-gemar
Treated with IPH5301 for 27 months from DL1 up to DL3



Pt 1003-Baseline



Pt 1003- M20; PR (-32%)



CONCLUSIONS

•IPH5301, up to the highest tested dose, was safe and well-tolerated with preliminary signals of monotherapy antitumor activity.

•Combination of IPH5301 with paclitaxel-trastuzumab is currently explored in the expansion part of the study in HER2-positive advanced breast and gastric cancer patients.

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