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A first-in-human phase I study of IPH5301, an anti-CD73 monoclonal antibody, alone or in combination with chemotherapy and trastuzumab, in patients with advanced solid tumors (CHANCES)

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BACKGROUND

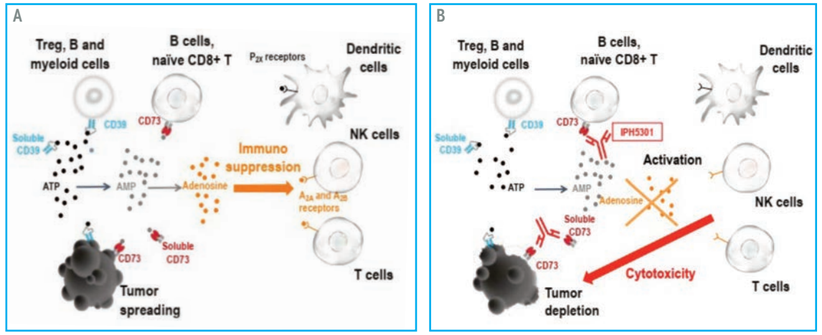
CD73

- CD73 is an extracellular ectonucleotidase overexpressed in the tumor microenvironment (TME) of multiple cancers.
- 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.

IPH5301

- IPH5301 is an 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: Mechanism of Action



STUDY DESIGN

- A multicentre, european, first-in-human, phase I study including 2 parts.

Part 1: a dose-escalation cohort enrolling up to 15 patients of selected cancer types to define RP2D of IPH5301 as single agent using a modified continual reassessment method (CRM, O'Quickley et al., Biometrics 1990).

Part 2: an expansion cohort enrolling 12 evaluable patients (6 patients with HER2+ breast cancer and 6 patients with HER2+ gastric cancer) to define RP2D of IPH5301 in combination with weekly paclitaxel-tratuzumab (3+3 design).

OBJECTIVES

Primary Objectives

- To evaluate the **safety profile**, to determine the **maximum tolerated dose (MTD) of IPH5301 alone** (dose-escalation part) and to **recommend a dose of IPH5301 to be administered in combination with chemotherapy** and trastuzumab in patients with selected advanced solid tumors in expansion part.

Secondary Objectives

- To characterize the pharmacokinetics of IPH5301 alone and in combination with chemotherapy and trastuzumab.
- To evaluate the preliminary clinical activity of IPH5301 alone and in combination with chemotherapy and trastuzumab.
- To determine the immunogenicity of IPH5301 alone and in combination with chemotherapy and trastuzumab.

Exploratory objectives

- Blood and tumor pharmacodynamics; serum cytokine release.

MAIN ELIGIBILITY CRITERIAS

- Prior treatment with at least one prior systemic therapy in the advanced metastatic setting.

a. Dose-escalation: breast, gastric, oesophageal, pancreatic, lung, endometrium or ovarian cancers with no limit on number of prior systemic therapies and considered as failing standard therapeutic alternatives and candidate to a phase I study by a multi-disciplinary tumor board.

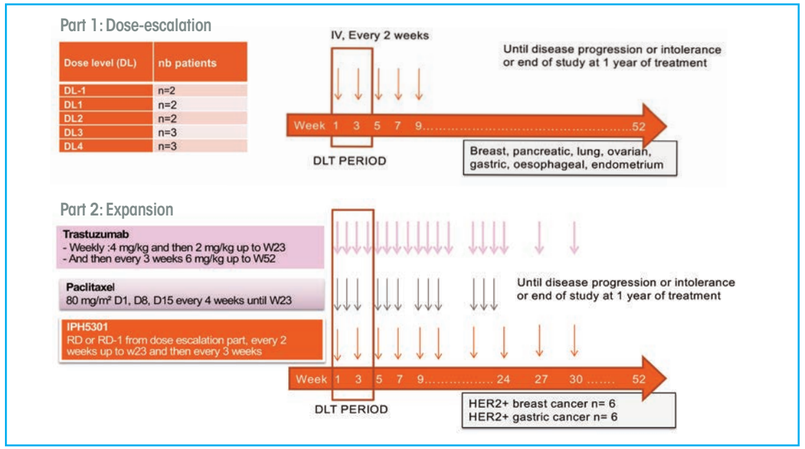
b. Cohort expansion: patients must have previously received (or be considered as non-eligible to) **all authorized standard treatments.**

- Breast cancer: patient must have received prior (or be considered as ineligible to) trastuzumab pertuzumab, trastuzumab emtansine, trastuzumab deruxtecan and capecitabine+anti-HER2 (trastuzumab, lapatinib ortrastuzumab tucatinib) **according to label.**
- Gastric cancer: patient must have received (or be considered as ineligible to) prior treatment with platinum salts and trastuzumab.

- ECOG-OMS PS 0-1
- Measurable disease according to RECIST1.1
- Adequate liver, renal and hematological functions.
- Asymptomatic and treated CNS lesions are eligible provided that no recent SRS, WBRT or neurosurgery and no need for steroids and other RECIST1.1 lesions are present outside CNS.

TREATMENT SCHEDULE

Figure 2: Treatment schedule



ENDPOINTS

Primary endpoints

- The occurrence of dose limiting toxicity (DLT) of IPH5301 in monotherapy in the dose escalation cohort.
- The recommendation of a dose of IPH5301 to be tested in combination with paclitaxel and trastuzumab in expansion part.
- The occurrence of DLT in patients who received the recommended dose of IPH5301 in combination with paclitaxel and trastuzumab in the expansion cohort.

Secondary endpoints

- PK of IPH5301
- Antitumor activity endpoints using RECIST version 1.1= Objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), and progression-free survival (PFS).
- Immunogenicity of IPH5301 endpoints: the number of subjects that develop anti-drug antibodies (ADA).

Exploratory

- PD biomarkers = receptor saturation, expression and activity in blood and tumors (for expansion only) ; predictive biomarkers at baseline for antitumor activity and cytokine release.

STUDY STATUS

- Enrollment ongoing in Marseille, France. Lille (France) and Bruxelles (Belgium) site activation is planned.

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AG has no conflict of interest to declare