OPTIMIZE-1, AN OPEN-LABEL PHASE 1B/2 STUDY ASSESSING THE SAFETY AND EFFICACY OF MITAZALIMAB IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA

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Background Mitazalimab is a human CD40 agonistic antibody (IgG1) developed for cancer immunotherapy. Targeting CD40 provides an opportunity to kickstart the cancer-immunity cycle by priming and activating tumor-specific T cells.^{1 2} Furthermore, the effects of CD40 agonists on myeloid cells promote degradation of the tumor stroma, improving the influx of T cells and chemotherapeutic agents into the tumor.¹ Targeting CD40 with mitazalimab in pancreatic ductal adenocarcinoma (PDAC), which is defined by a desmoplastic tumor stroma that hosts immune-suppressive macrophages, has the potential to augment responses to chemotherapy, initiating an effective anti-tumor immune response. Data from a phase 1 study (NCT02829099) demonstrated early signs of clinical activity in solid tumors with one partial response and SD in 37% of the patients.³ Mitazalimab was safe and tolerable at intravenous doses up to 1200 µg/kg and most drug-related adverse events were grade 1 or 2.³ Biomarker data from this study demonstrated proof of mechanism, validating mitazalimab's ability to activate CD40 in cancer patients. In preclinical hCD40tg mouse models, repeated administration of mitazalimab in combination with FOLFIRINOX induced a long-term survival when compared to chemotherapy alone.⁴

Methods OPTIMIZE-1 is a phase 1b/2, open-label, multicenter study designed to evaluate safety, tolerability, and efficacy of mitazalimab in combination with chemotherapy (mFOLFIRINOX) in adults diagnosed with previously untreated metastatic PDAC. Mitazalimab and mFOLFIRINOX will be administered by intravenous infusions following a 14-day cycle schedule where mitazalimab will be administered 2 days after mFOLFIRINOX, except for the first cycle of 21 days where mitazalimab will be administered on Day 1 and 10 and infusion of mFOLFIRINOX will start Day 8. In Part 1 (Phase 1b) of the study, the dose of mitazalimab will be escalated from 450 µg/kg to 900 µg/kg (2 dose levels to be evaluated) to obtain the recommended phase 2 dose (RP2D). Part 1 follows a Bayesian optimal interval design (BOIN) with at least 3 patients enrolled at each dose level. A minimum of 6 patients will be evaluated at the RP2D. In Part 2 of the study, the RP2D of mitazalimab will be administered in combination with mFOLFIRINOX to all patients. The study expansion will evaluate the clinical efficacy of mitazalimab in combination with mFOLFIRINOX assessing objective response rate (ORR) (primary endpoint), Progression-free survival (PFS) and Overall survival (OS) (secondary endpoints). The study expansion includes a Simon's two-stage design with an interim analysis to allow stopping for futility or efficacy based on ORR.

Trial Registration NCT04888312

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Ethics Approval The study was approved 19 July 2021 by CHU UCL Namur, site Godinne Comité d'éthique Avenue Docteur G. Thérasse 1 5530 YVOIR, Belgium, approval number 32/2021 and 2 July 2021 by Comité de Protection des Personnes EST I, France, approval number SI2G 21.00648.677157

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