The RELEASE trial - PhotoChemical Internalization (PCI) with Gemcitabine in Extrahepatic Cholangiocarcinoma (CCA) Added to Standard Gemcitabine and Cisplatin Chemotherapy

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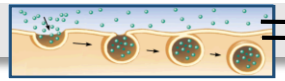
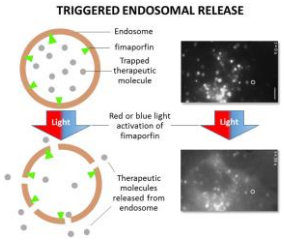
PCI, mode of action

- PhotoChemical Internalization (PCI) is a novel technology based on a chemical reaction which can be triggered in a controlled manner
- The reaction is based on the administration of a photosensitizer, fimaporfin, administered locally or as an intravenous injection
- Fimaporfin is inert and has no effects of its own until it is reached by light of a specific wavelength (red or blue light), which can be produced by a laser
- When fimaporfin has been taken up by cells in a diseased tissue, a local reaction can be triggered by illumination with laser light directed at the target disease tissue, e.g. a tumor
- This triggers the photochemical reaction to instantly occur, and only in the very close vicinity of each fimaporfin molecule

PCI targets endosomes



- In cancer (and normal) cells, various compounds are engulfed from the cell surface into the cells to form small vesicles, called endosomes. In these endosomal vesicles, cells can contain, process, or eliminate various substances



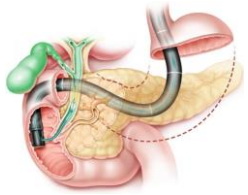
- Fimaporfin is designed to end up on the inside of the membrane of the endosomes within the cell
- Upon illumination with the laser light, the endosomes inside cells are destabilized and becomes leaky, losing their contents of therapeutics which then more easily can reach their intended target within the cell

- Chemotherapeutics and vaccines have been evaluated in clinical trials with PCI and are in further development

Gemcitabine is well suited as a chemotherapeutic drug that could be optimized by the combination with PCI

PCI with gemcitabine in extrahepatic CCA

- Gemcitabine is established as standard-of-care in extrahepatic cholangiocarcinoma treatment in combination with cisplatin (gem/cis cyclic treatment)



- In extrahepatic CCA, the laser light can be targeted locally right at the tumor during an endoscopic (ERCP) or transhepatic (PTC) standard procedure. A light transmitting fiber is placed in the bile duct and the laser light application procedure takes about 5 -20 minutes depending on the size of the tumour. This treatment will trigger the PCI enhancement of gemcitabine locally

A safe and tolerable PCI dose (fimaporfin + light energy) in combination with gemcitabine was established in a phase I dose escalation trial

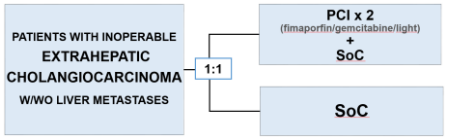
- No Dose-Limiting Toxicity (DLT) was observed, and no unexpected safety concerns detected
- Serious Adverse Events, primarily cholangitis, were similar in frequency, severity and the incidence pattern reported in gem/cis treated extrahepatic CCA
- Like other photosensitizers, fimaporfin caused transient light sensitivity but with no event reports of major concerns or severity
- The trial was extended to investigate two times PCI treatments during gem/cis cycles at the selected dose in the dose escalation trial: no additional safety signals have been detected
- A total of 23 extrahepatic CCA patients have been treated with either one or two PCI treatments in this trial

This trial showed an acceptable safety profile for PCI in extrahepatic CCA at all doses, and the limited but encouraging efficacy data has paved the way for the randomized pivotal study; the RELEASE trial

The RELEASE trial – recruiting patients

A pivotal multicenter, randomized, open label trial that are recruiting patients across multiple hospitals in Europe and in the US

- A total of 186 subjects will be included in this trial
- All subjects will receive the established standard-of-care treatment (SoC); gemcitabine and cisplatin in up to 8 Cycles
- Half of the patients will receive the experimental treatment with PCI in addition to the SoC. The PCI treatment procedure will be incorporated in the chemotherapy cycles at up to 2 occasions (Cycle 1 + Cycle 5)



Arm A: PCI treatment (fimaporfin + gemcitabine + laser application) at Cycle 1 and 5 as part of systemic gemcitabine/cisplatin treatment

Arm B: Systemic gemcitabine/cisplatin treatment alone

PCI treatment schedule

- STUDY POPULATION
  - Subjects with inoperable, extrahepatic previously untreated CCA. The CCA might have spread to the liver region.
- OBJECTIVES
  - To assess the efficacy of PCI with gem/cis treatment versus gem/cis alone
  - To further assess the safety of PCI with gem/cis treatment in extrahepatic CCA
- The RELEASE trial IN SUMMARY
  - Based on previous data, PCI incorporated into Gem/Cis standard-of-care is safe and tolerable, with encouraging early efficacy data
  - This pivotal trial is designed with registrational intent, and includes a formal interim analysis potentially qualifying for an accelerated approval
  - PCI added to standard-of-care chemotherapy at 1 or 2 occasions imply limited extra burden on caregivers and patients in the setting of a collaborative multidisciplinary teamwork
  - *If you have questions about PCI and this study, come and talk to us in our booth!*
  - *ClinGov reference: NCT04099888*

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