Photochemical internalization (PCI) of gemcitabine in locally advanced inoperable Cholangiocarcinoma - a new technique with promising clinical activity

Jörg Trojan, Universitätsklinikum Frankfurt

IPA Masterclass, 08. November 2021

Conflict of interest statement

Advisory role

Amgen, AstraZeneca, Bayer Healthcare, Bristol Myers-Squibb, Eisai, Insitute for Quality and Efficency in Health Care (IQWiG), Ipsen, Merck Serono, Merck Sharp & Dome, Lilly Imclone, PCI Biotech, onkowissen.de, Roche, Servier

Speakers honoraria

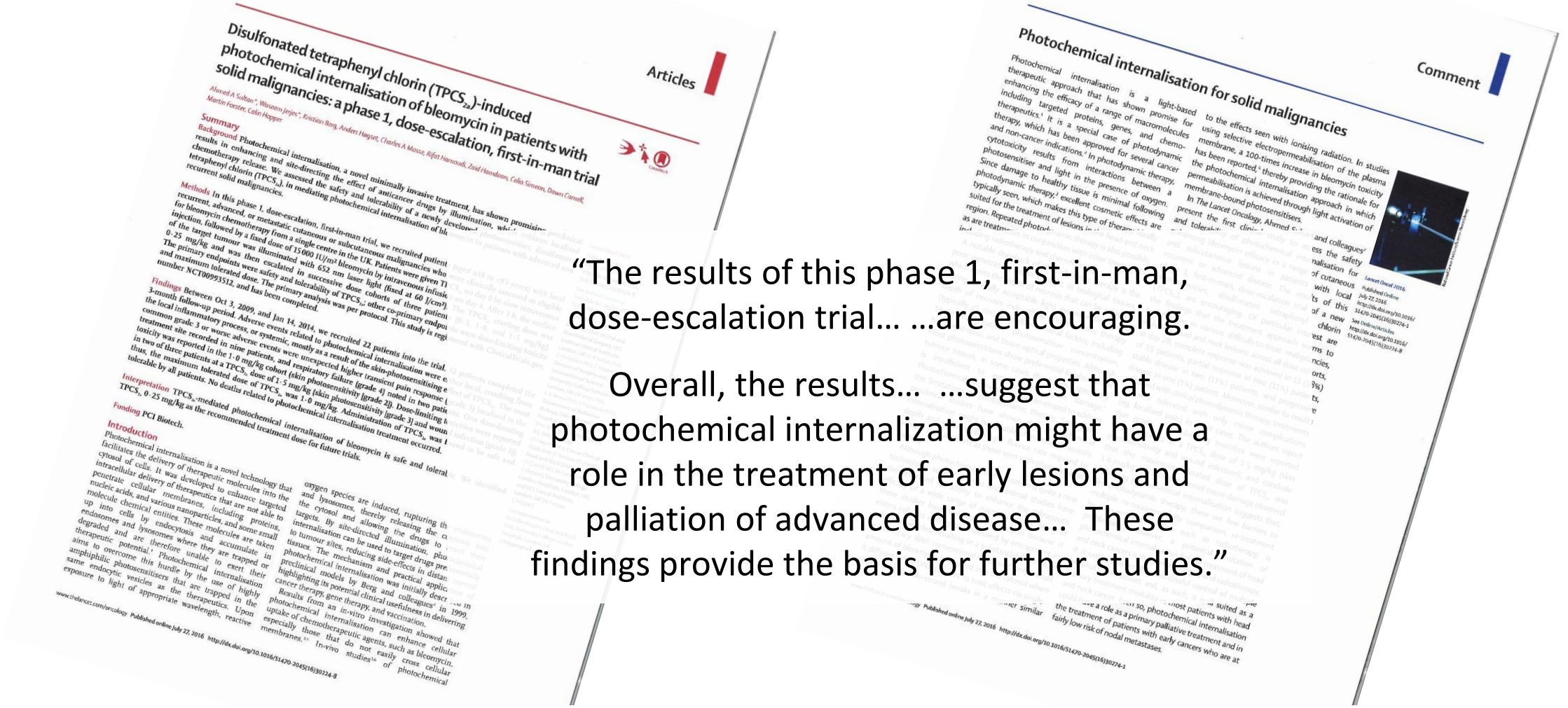
Amgen, Bayer Healthcare, Bristol Myers-Squibb, Daichi Sankyo, Eisai, Ipsen, Merck Serono, Merck Sharp & Dome, Lilly Imclone, Roche, Servier, streamedup!

Research grants

Ipsen, Roche

First-In-Man Study Published in Lancet Oncology[1]

- With independent expert commentary[2]



"The results of this phase 1, first-in-man, dose-escalation trial… …are encouraging.

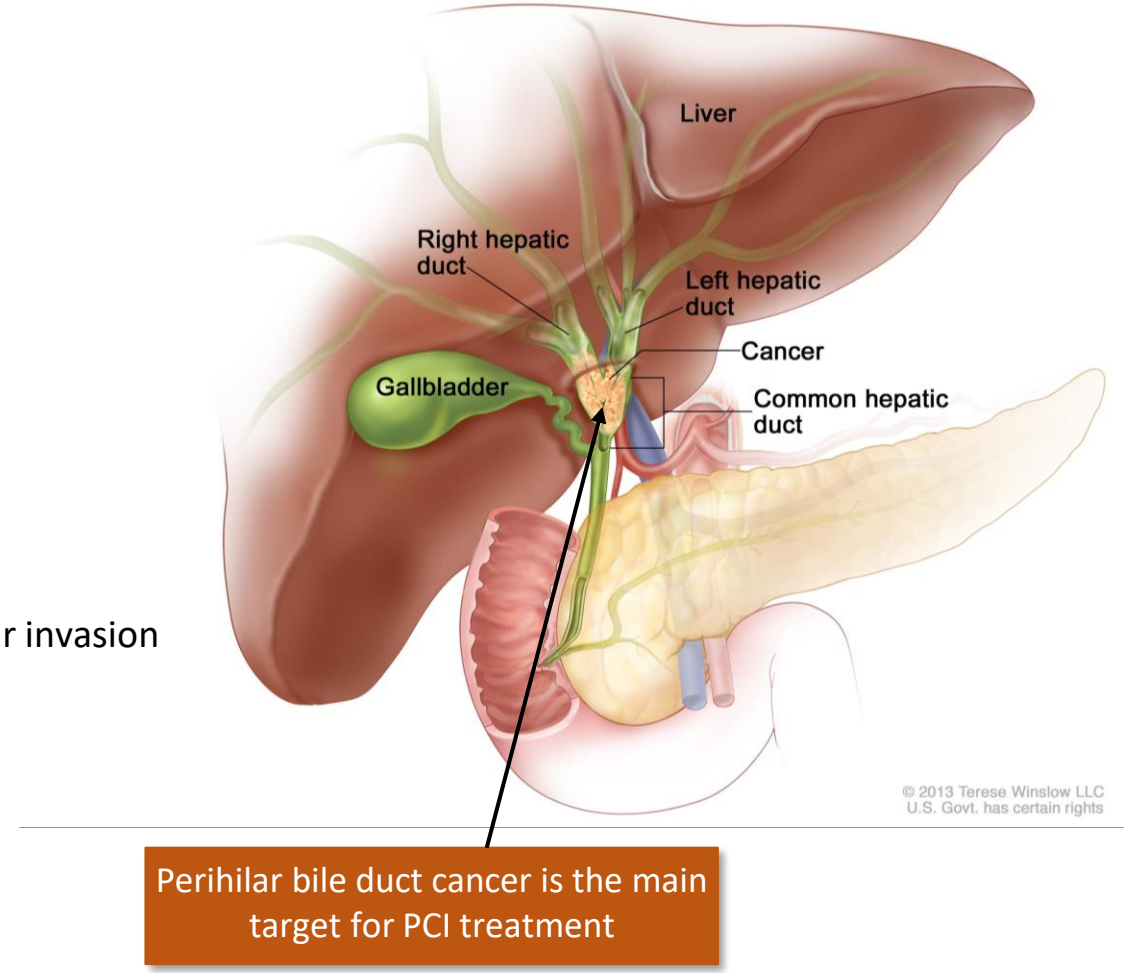
Overall, the results… …suggest that photochemical internalization might have a role in the treatment of early lesions and palliation of advanced disease… These findings provide the basis for further studies."

[1] Sultan et al (2016) Lancet Oncology 17(9):1217-1229
[2] Madsen (2016) Lancet Oncology 17(9):1173-1174

Bile Duct Cancer (Cholangiocarcinoma, CCA):

- Life threatening and poor outcomes

- Survival: Poor Prognosis
  - 5 years survival (Europe), 5% to 17% depending on CCA [1]
- Cholangiocarcinoma includes:
  - Intra-hepatic tumours (iCCA): 10%[1]
  - Extra-hepatic tumours
    - Perihilar/Klatskin tumours, (pCCA): 60-70%[1]
    - Distal tumours dCCA: 20-30%[1]
- Classification based on different evolving systems[2]:
  - Primary tumours, localisation, size/number, accessibility, vascular invasion
  - Regional lymphatic nodes and distant metastasis
- Diagnosis: no straightforward clinical features
  - Peak age for CCA is the seventh decade
  - Late stage and rapid deterioration



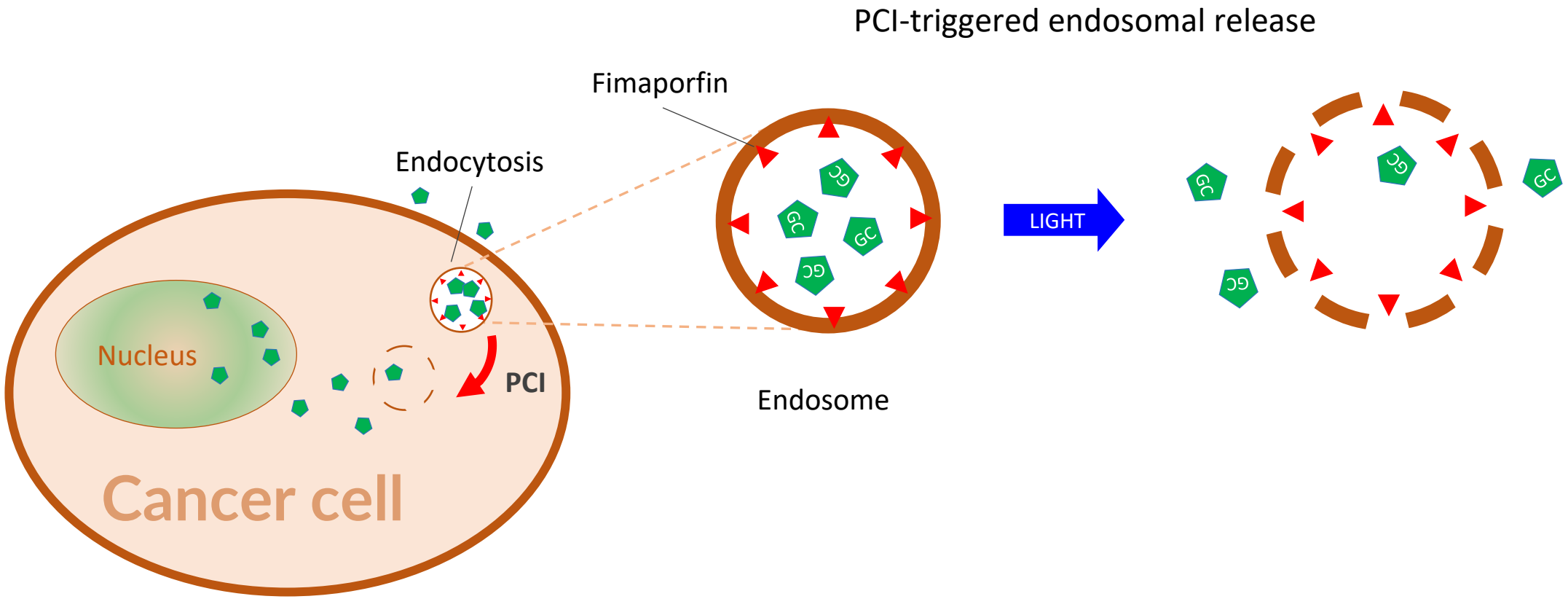
Perihilar bile duct cancer is the main target for PCI treatment

1) Rare care project 2) ESMO clinical practices guidelines, 2016

Bile Duct Cancer – PCI Treatment

Three step treatment procedure

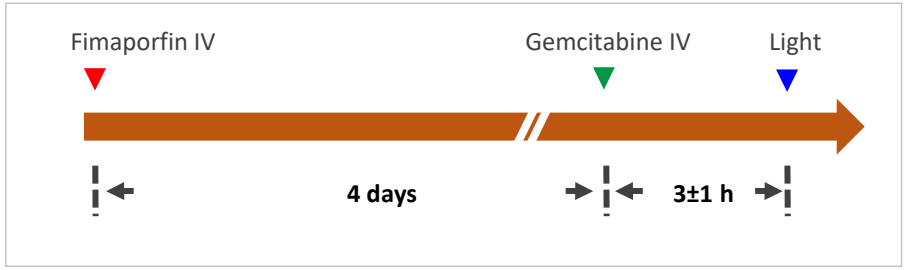
- The aim is to increase the treatment effect of gemcitabine by increasing intracellular gemcitabine concentration
- Fimaporfin is a photosensitiser that is inert until activation by light (652 nm)



Bile Duct Cancer – PCI Treatment

- Three step treatment procedure

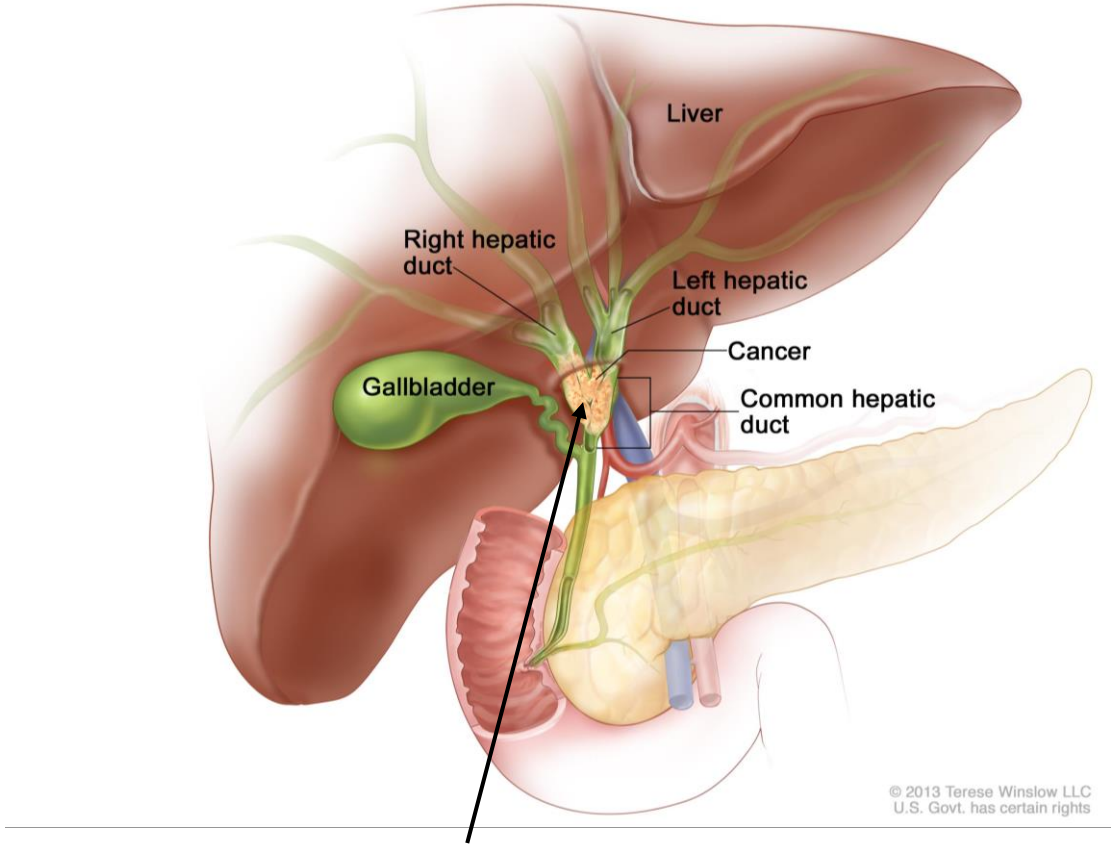
- PCI Treatment in CCA/bile duct cancer



Three step PCI treatment procedure:

- Fimaporfin injection
- Gemcitabine infusion
- Illumination as a short add on procedure during standard ERCP

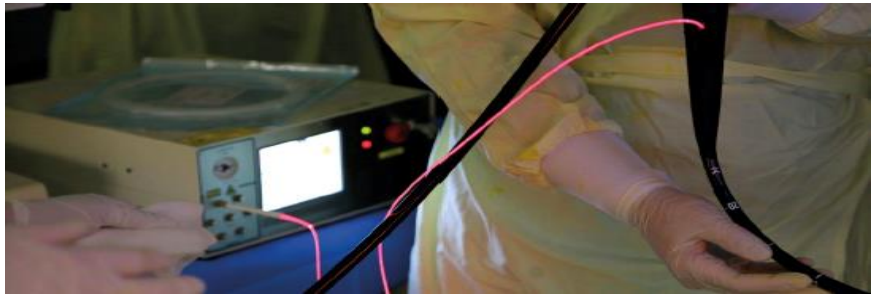
- Main aim for PCI treatment in CCA is to enhance the effect of gemcitabine locally at the tumour target



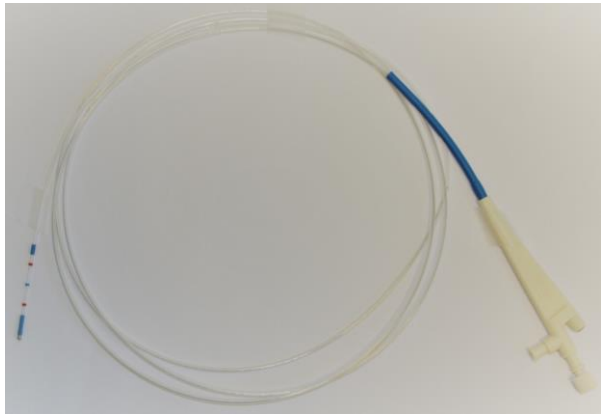
Perihilar bile duct cancer is the main target for PCI treatment

PCI treatment procedure

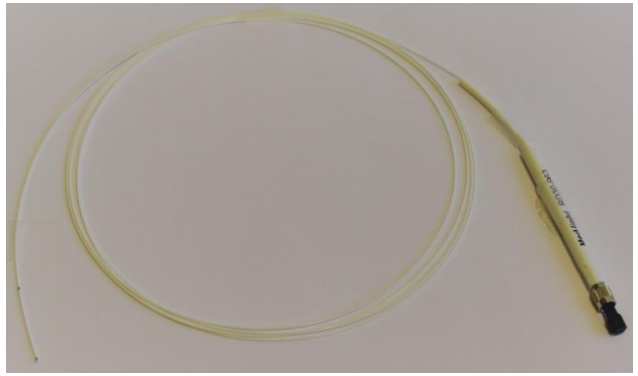
- Laser treatment

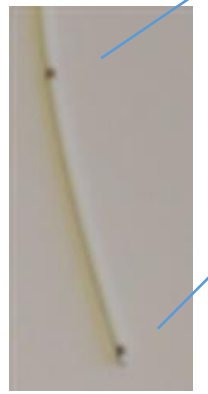


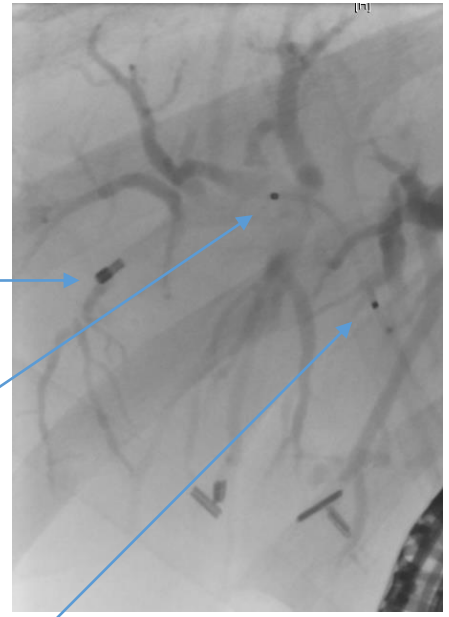
catheter



cylindrical light diffuser







Bile Duct Cancer – Phase I Study

- Patient population

- Phase I dose escalation (different doses of light and fimaporfin) : 16 patients
- Phase I extension (up to two PCI treatments) : 7 patients were included
- Patients included were
  - locally advanced cholangiocarcinoma with stenosis in the perihilar or distal region
  - treatment naïve
  - adenocarcinoma
  - ECOG 0-1
  - stented

Bile Duct Cancer – Phase I Study

- Safety and Phase II recommended dose established

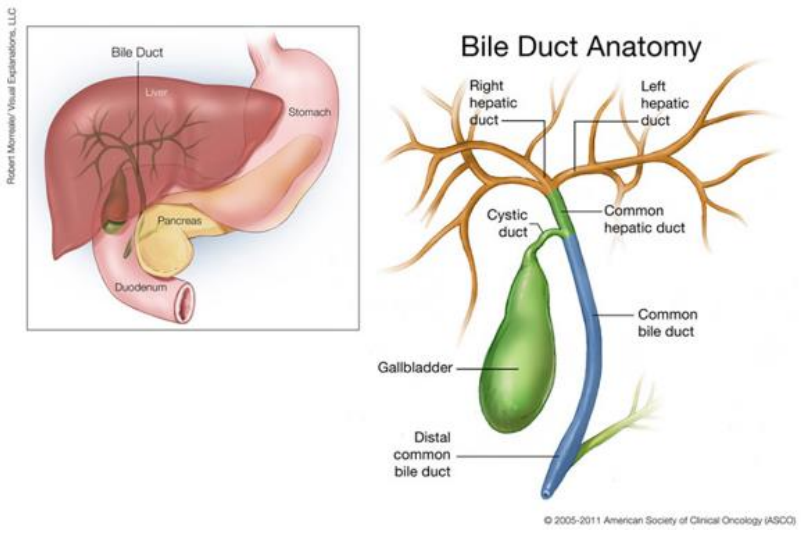
- Dose escalation with one PCI treatment, followed by an extension part for safety of two PCI treatments

<u>Dose escalation part (N=16)</u>

- Standard 3+3 design, with one PCI treatment
- 4 dose escalation cohorts
- No Dose-Limiting Toxicity (DLT) were observed
- No unexpected safety concerns
- Serious Adverse Events (SAEs) primarily cholangitis, similar to the frequency, severity and pattern reported in the literature for perihilar bile duct cancer
- Transient light sensitivity from PCI treatment considered acceptable in context of the encouraging signs of anti-tumour activity

<u>Extension part (N=7)</u>

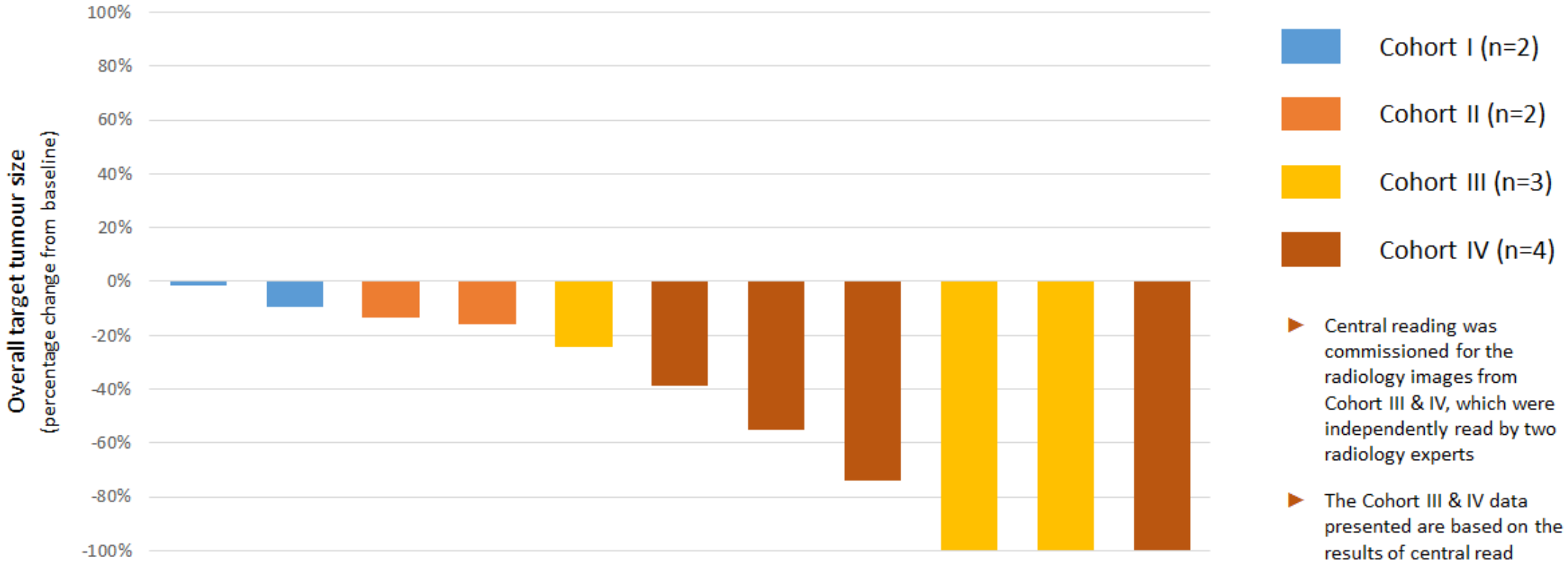
- Explored safety of two PCI treatments (N=5)
- Same dose as dose escalation cohort IV, but up to two treatments
- No new safety signals



Bile Duct Cancer – Phase I Dose Escalation Results

- Early signs of anti tumour activity – 11 evaluable patients of 16 included

All radiologically evaluable patients from all dose escalation cohorts in Phase I



Bile Duct Cancer – Phase I Dose-Escalation Study

- Early signs of anti tumour activity – median Overall Survival of 22.8 months at selected dose

Parameters	Cohort IV (N=6)	Phase I – all dose-escalation cohorts (N=16)
Median Overall Survival (mOS)	22.8 months	15.4 months

- Study closed and Cohort IV dose selected for the pivotal RELEASE trial
- Encouraging Phase I results paved the way for a pivotal trial, with potential for accelerated approval
- No new safety signals with two treatments in the Phase I Extension – up to two treatments allowed in RELEASE

Case Study Report from 3 patients

- Dechene et al 2020
- Endoscopy International Open

Published online: 2020-11-27

Innovation forum

Photochemical internalization and gemcitabine combined with first-line chemotherapy in perihilar cholangiocarcinoma: observations in three patients

OPEN ACCESS

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ABSTRACT

Photochemical internalization (PCI) is a technology to induce a localized, intracellular enhancement of therapeutics that are processed through endosomal pathways, including gemcitabine in malignant cells. In addition to a direct phototoxic and tumoricidal effect, PCI specifically disrupts endosomal membranes and, thereby, the compartmentalization of certain cytotoxic compounds to enhance a drug's intended intracellular target reach within the tissue treated. Non-resectable extrahepatic cholangiocarcinoma (eCCA) is a common primary tumor and gemcitabine/cisplatin chemotherapy is widely considered standard of care for it. PCI is well suited as an endoscopic intervention, and clinical observations in three subjects participating in a phase I/IIa dose escalation safety trial are described. The trial included patients with perihilar, non-resectable CCA suitable for standard-of-care chemotherapy. Per protocol, a single endoscopic PCI procedure with gemcitabine was conducted at the initiation of standard gemcitabine/cisplatin therapy. Sixteen patients enrolled in the initial dose escalation phase of the trial, which later was extended to explore the safety of a second PCI procedure during chemotherapy.

While limited to a case series, the various clinical observations described here serve to illustrate the effects of localized, perihilar tumor targeting in appropriate patients by any safe methodology, including PCI. As previously indicated by clinical data using other localized treatment modalities, adding a directed, tumor-targeting treatment to systemic therapy to ameliorate the progressively expanding extrahepatic tumor burden can have important effects on the overall outcome of systemic treatment in many patients who have incurable eCCA.

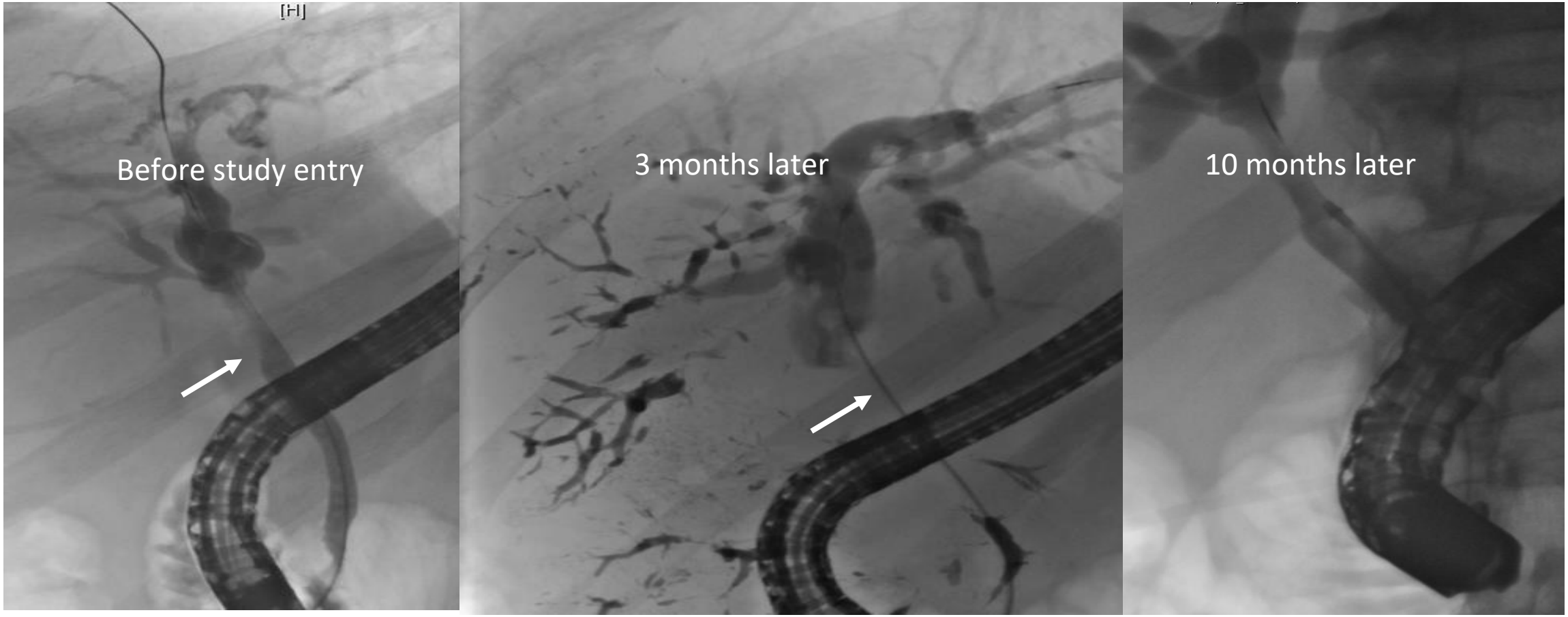
Introduction

Perihilar cholangiocarcinoma (CCA) is an adenocarcinoma with variable histological characteristics arising from the proximal portion of the common bile duct, including the main left or right hepatic ducts or their confluence. Surgical resection is the only curative option, but because early symptoms are infrequent, most patients present with obstructive jaundice or cholangitis on the basis of a primarily non-resectable, advanced-stage tumor and an expected survival of 6 to 12 months [1, 2]. Standard of care is biliary drainage and systemic therapy, most often gemcitabine/cisplatin chemotherapy, resulting in a median overall survival of almost 12 months [3].

E1878

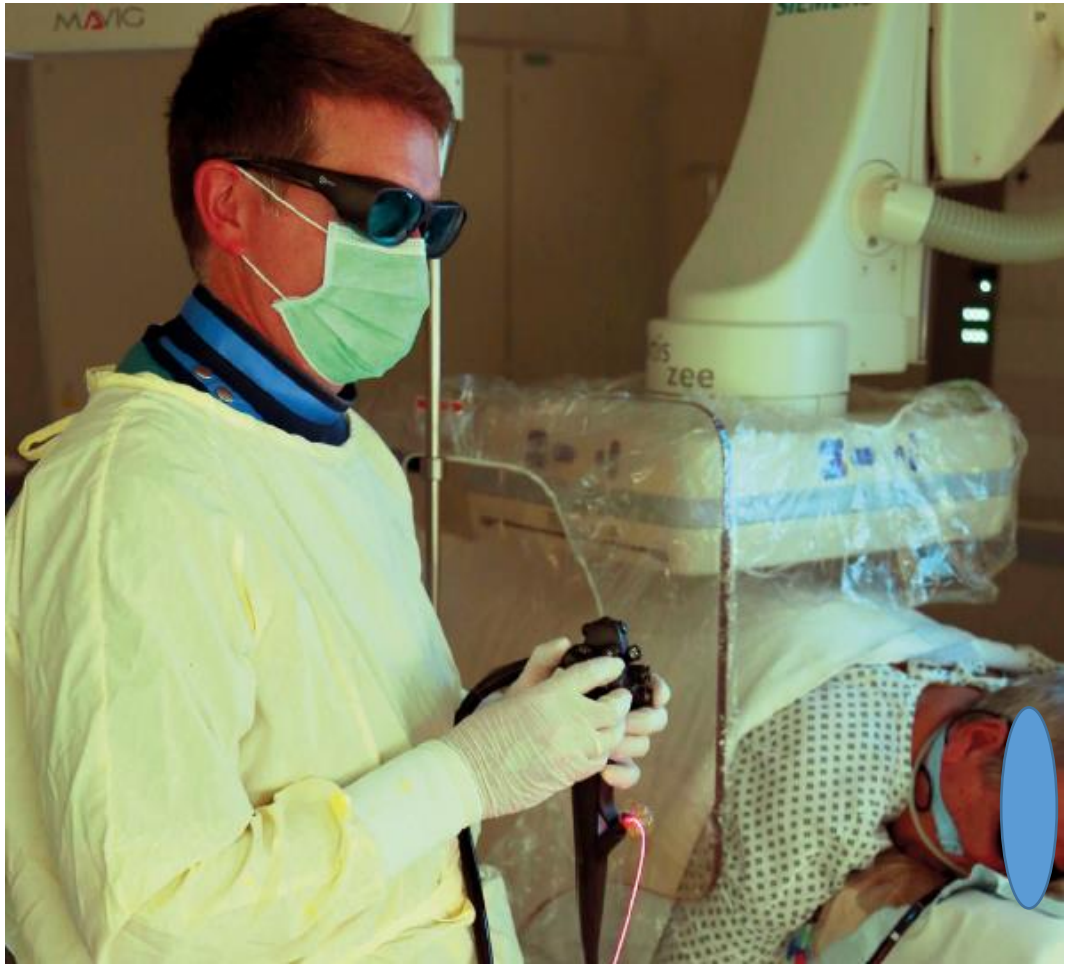
Dechêne Alexander et al. Photochemical internalization and … Endoscopy International Open 2020; 08: E1878–E1883 | © 2020. The Author(s).

Case report 2



- **Patient – male 78 years old – 7 cycles of chemotherapy and one PCI treatment**

Case report summary

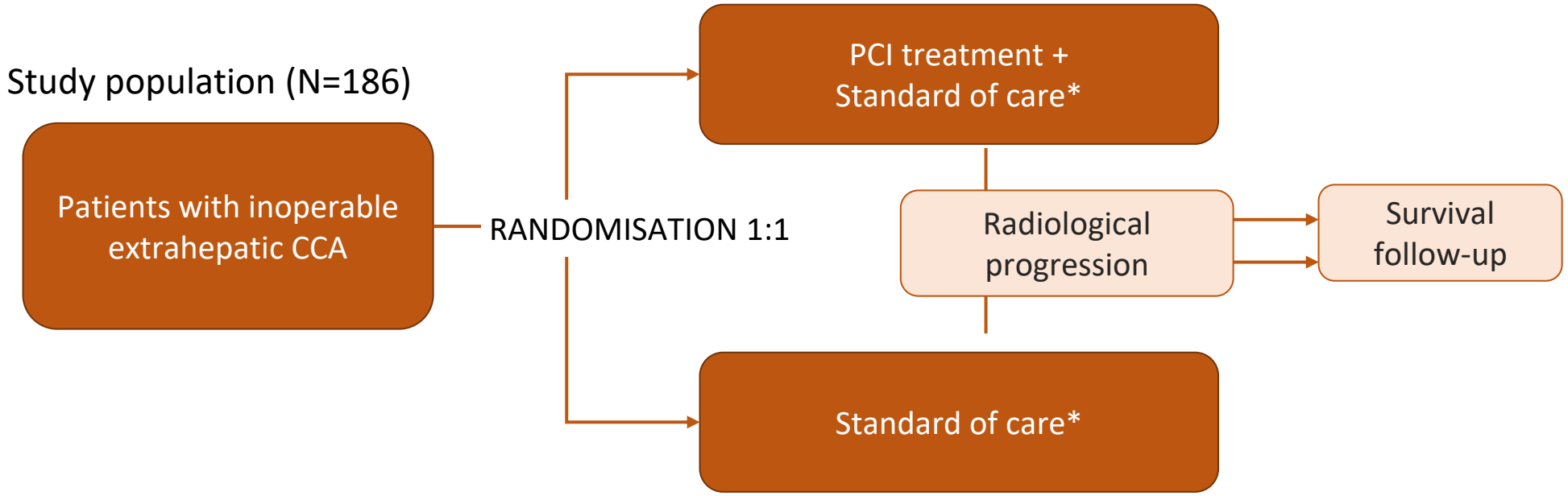


- No bleeding episodes (in contrast to intraductal RFA)
- PFS of PCI with Gem followed by GemCis is very promising
- Two rounds of PCI might further enhance this benefit

Bile Duct Cancer – Release Study

- RELEASE study are currently recruiting for patients

- Study design



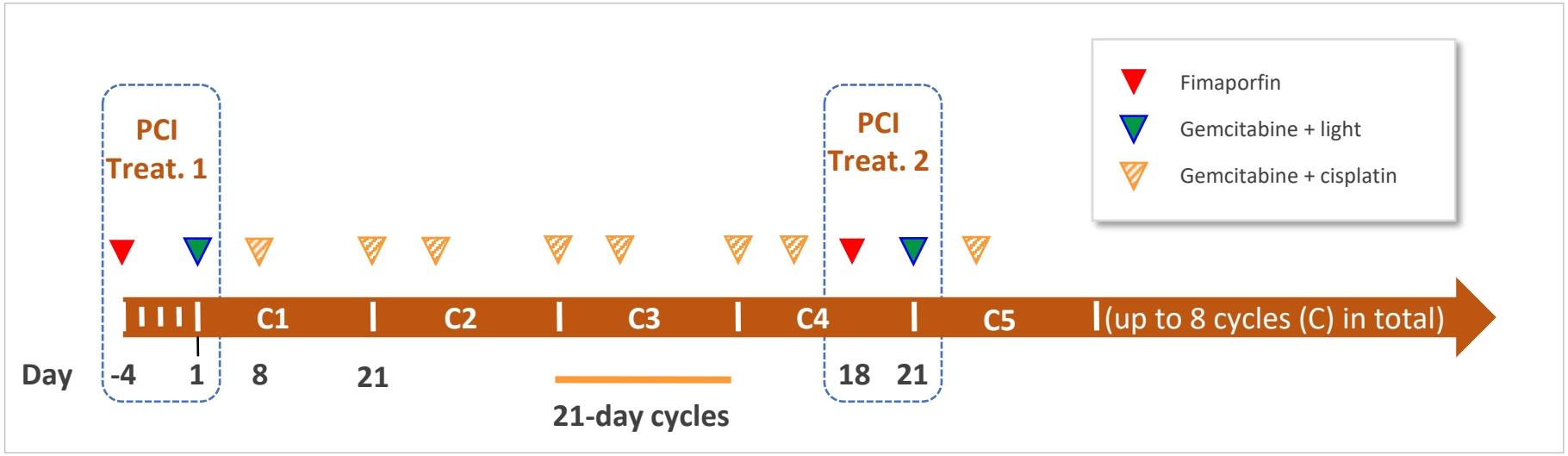
* SoC – up to 8 cycles of gemcitabine and cisplatin

Endpoints
Primary: PFS
Secondary: OS, ORR, other

ClinicalTrials.gov Identifier: NCT04099888

Bile Duct Cancer – Release Study

Up to 2 PCI treatments in RELEASE incorporated into the SoC of gemcitabine and cisplatin



ClinicalTrials.gov Identifier: NCT04099888

Bile Duct Cancer – Release Study

- Patient population

- Inoperable cholangiocarcinoma
- Perihilar or distal stenosis requiring stenting
- Adenocarcinoma
- Metastatic disease is allowed (except for bone and CNS)
- At least one radiological lesion that is measurable or evaluable by RECIST
- Eligible for gemcitabine and cisplatin treatment
- Up to 2 cycles of gemcitabine + cisplatin may have been initiated before study entry
- Adequate biliary drainage (up to 5 x ULN of bilirubin is acceptable)
- ECOG 0-1

ClinicalTrials.gov Identifier: NCT04099888

Bile Duct Cancer – Release Study

- Status

- 47 sites active for recruitment in Europe, USA and Asia
- FPFV May 2019 (Europe)
  - First patient in Asia Oct 2020
  - First patient in USA Apr 2021
- https://clinicaltrials.gov/ct2/show/NCT04099888